


# HISTORY OF THE SECOND WORLD WAR

## UNITED KINGDOM MEDICAL SERIES

Editor-in-Chief

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# MEDICAL RESEARCH

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# FOREWORD

THIS volume of the Official Medical History of the War of 1939–45, edited by Dr. F. H. K. Green and Sir Gordon Covell, describes the researches in medical science promoted by the Medical Research Council and by various Government Departments during those eventful years. Special thanks are due to Dr. Green for his interest and labours, not only in the recording of the Council's work but also in the collation and selection of material for the History from 1941 onwards.

The striking part which the Council (then the Medical Research Committee) played in the alleviation of suffering and the application of new methods to the diagnosis and treatment of disease in the First World War are still remembered and owed much to the initiative and direction of the Council's first Secretary, Sir Walter Fletcher. This tradition was ably maintained in the Second World War by his successor, Sir Edward Mellanby, who also rendered great assistance to this History as a representative of the Medical Research Council on the Editorial Board.

During the war the work of the Medical Research Council was directed into new courses to serve the national effort, and as a result it was also greatly expanded in volume. In the first place, the attention of the Council's research workers was largely turned to war problems which had assumed immediate practical importance. Illustrative examples are the treatment of burns, malarial research, nutrition in war-time and the development of penicillin. In the second place the Council were called upon more than ever before to give scientific advice and assistance to administrative Government Departments and to the Defence Services. In the third place the Council also undertook the organisation and direction of certain emergency services of a technical nature, for example the Emergency Public Health Laboratory Service and the Blood Transfusion Service.

Abundant evidence will be found in this volume to show how great were the advances in medical science made before and during the late war. Every picture has its light and shade and it is a relief to turn from the sombre background of death and destruction to the light and glory of the conquest of pain and disease which medical research has painted in the foreground of the war picture.

ARTHUR S. MACNALTY
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# PREFACE

THE purpose of this volume is to give a conspectus of officially sponsored medical research by British investigators during the War of 1939–45, in so far as the work was directly related to the war effort. Research on problems of more general medical interest, such as fundamental research in physiology and biochemistry or research on cancer, is not discussed; nor has it been possible to include all the work bearing on the war effort which was done under non-official auspices. It should be emphasised that the volume is not exclusively a history of the war work of the Medical Research Council, though descriptions of the many research activities initiated and supported by the Council naturally form a large part of its content; it deals also with some investigations promoted directly by the Fighting Services and by certain Government Departments. Research by workers in the universities is in general mentioned only when it formed part of a scheme supported or co-ordinated by the Medical Research Council, or was carried out on behalf of a Government Department.

A guiding principle in compiling this volume has been to describe even the most important research work as concisely as possible if it has been fully reported elsewhere. This has inevitably made for some inequality of scale between the different sections, but it was considered preferable to attempting to repeat the technical details of published researches. Lists of scientific papers dealing with the work described are given at the ends of the chapters; these lists also include large numbers of publications relating to work not specifically mentioned in the text. The task of collecting and checking the many references to publications has been formidable and it is not claimed that the lists are complete; apologies are due to the authors of important studies which may inadvertently have been omitted. It should be made clear that the references to publications are intentionally almost confined to British work. Only a very few publications by investigators in other Commonwealth countries, the United States and elsewhere are mentioned. This means, of course, that the lists of publications at the ends of the chapters are by no means a comprehensive record of all the important work published on the particular subjects during the war; they should, however, include most of the major research contributions by workers in the United Kingdom or with the British forces oversea.

Examples of British war-time researches of medical interest which were organised by bodies other than the Medical Research Council are the studies in defence against chemical warfare agents, which were mainly a concern of the Ministry of Supply (Chapter 10), and the

experimental work on the biological effects of explosions, with special reference to air-raid dangers, which was sponsored by the Ministry of Home Security (Chapter 11, Part I); the latter is reported here in greater detail than are most of the subjects dealt with in the other chapters, since the major part of it has not been published independently.

Certain omissions from this volume call for explanation. There is little or no mention of the war-time researches in psychiatry, the reason being that the subject was considered to be adequately covered in other volumes of the Official Medical History. The same applies to war-time advances in anaesthesia and in technical methods of surgery, including new methods for the plastic repair of wounds and burns; the remarkable practical achievements of British workers in these fields are described in the clinical volumes. The important subject of personnel selection for the Fighting Services is mentioned here only in so far as it was a concern of the Medical Research Council or of the Flying Personnel Research Committee of the Air Ministry.

Much of the text of this volume is closely similar to that of the Report of the Medical Research Council for 1939–45, which was published in 1948 under the title *Medical Research in War*. Comparison of the two books will show, however, that they have considerable differences of content. Thus, the Report of the Council deals not only with studies which had a direct bearing on the war effort, but also with the fundamental work in medical science which was supported by the Council during the war period. Apart from the chapters on chemical defence research and on the biological effects of explosions, to which reference has been made above, the largest single contribution to this volume from sources other than the Medical Research Council is a report from the Air Ministry on the work of the Flying Personnel Research Committee, which has been incorporated in Chapter 2. The accounts of many other investigations described only briefly in the Council's Report have here been amplified with the generous help of the workers concerned.

# ACKNOWLEDGMENTS

THE greater part of the contents of this volume is derived from the Reports of the Medical Research Council for 1938–9, 1939–45 and 1945–8, but its expansion to the present form, with references to publications, would not have been possible without the help freely given by many people. The names of those who kindly provided draft sections or assisted materially with constructive criticism are printed below, with a list of the subjects of their contributions or advice.

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| 2 | Surgeon Commander F. P. Ellis, O.B.E., M.D., M.R.C.P., R.N. | The work of the Royal Naval Personnel Research Committee |
| | Professor F. A. E. Crew, M.D., D.Sc., F.R.C.P.Ed., F.R.S. | The Directorate of Biological Research, War Office |
| | Miss I. M. Marshall (Air Ministry) | The work of the Flying Personnel Research Committee |
| 3 | Sir Percival Hartley, C.B.E., M.C., D.Sc., F.R.S. | Anaerobic wound infections |
| | A. A. Miles, F.R.C.P. | Anaerobic wound infections |
| | Miss M. G. Macfarlane, D.Sc., Ph.D. | Anaerobic wound infections |
| | J. V. Dacie, M.B., M.R.C.P. | Anaerobic wound infections |
| | R. E. O. Williams, M.D., B.Sc. | The prevention and treatment of wound infections in general |
| | Professor P. B. Medawar, M.A., D.Sc., F.R.S. | The biologist's contribution to wound treatment |
| | Professor Sir James Learmonth, K.C.V.O., C.B.E., Ch.M., F.R.C.S., F.R.S.E. | Injuries to blood vessels; immersion limb |
| | Raymond Greene, D.M., M.R.C.P. | Frostbite |
| | Professor E. D. Adrian, O.M., M.D., F.R.C.P., P.R.S. | Brain injuries |
| | Norman M. Dott, C.B.E., M.B., F.R.C.S.E. | Brain injuries |
| | Professor Sir Geoffrey Jefferson, C.B.E., M.S., M.B., F.R.C.S., F.R.C.P., F.R.S. | Brain injuries |
| | W. Ritchie Russell, M.D., F.R.C.P. | Brain injuries |
| | H. J. Seddon, D.M., F.R.C.S. | Nerve injuries |
| | Professor J. McMichael, M.D., F.R.C.P. | Traumatic shock |

| | | |
|---|---|---|
| | Professor A. C. Frazer, D.Sc., M.D., F.R.C.P. | Fat embolism |
| | D. P. Cuthbertson, D.Sc., M.D., F.R.S.E. | Metabolic effects of injury |
| | P. L. Mollison, M.D., M.R.C.P. | Blood transfusion, blood grouping and blood products |
| | W. d'A. Maycock, M.D. | Blood transfusion, blood grouping and blood products |
| | J. H. Humphrey, M.D. | Blood group substances |
| 4 | Charles Newman, M.D., F.R.C.P. | Dyspepsia in the Army, 1939–40 |
| | P. D'Arcy Hart, M.D., F.R.C.P. | Tuberculosis |
| | G. S. Wilson, M.D., F.R.C.P., D.P.H. | Tuberculosis (part) |
| | Professor J. W. S. Blacklock, M.D., F.R.F.P.S. | Tuberculosis (part) |
| | W. D. W. Brooks, D.M., F.R.C.P. | Pulmonary tuberculosis in the Fighting Services |
| | C. H. Andrewes, M.D., F.R.C.P., F.R.S. | Influenza |
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| 5 | Miss E. M. M. Hume, M.A. | Nutrition and malnutrition |
| | Professor S. J. Cowell, M.B., F.R.C.P. | Studies of malnutrition |
| | Professor J. Beattie, M.D. | Studies of malnutrition (part) |
| | J. H. Walters, M.D., M.R.C.P. | Marasmus among Indian prisoners-of-war |
| 6 | Professor R. Cruickshank, M.D., F.R.C.P., D.P.H. | Air hygiene and the prevention of cross-infection |
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| 7 | F. Hawking, D.M., D.T.M. | War-time research on the sulphonamides |
| | D. G. Ardley, Esq. | War-time research on the sulphonamides |
| 8 | R. S. F. Schilling, M.D., D.P.H. | Industrial health research |
| | J. N. Agate, M.D., M.R.C.P. | Industrial health research |
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| | E. Chain, Ph.D., F.R.S. | The chemistry of penicillin |
| 10 | Ministry of Supply | Chemical defence research |
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| | M. Dixon, Sc.D., F.R.S. | Chemical defence research |
| 11 | Professor S. Zuckerman, C.B., D.Sc., M.D., F.R.S. | The biological effects of explosions |
| | Professor G. R. Cameron, D.Sc., F.R.C.P., F.R.S. | Underwater blast |

The following are among those who provided drafts used in the Report of the Medical Research Council for 1939–45, which have been adapted for the purpose of this volume:

| | |
|---|---|
| Professor G. L. Brown, C.B.E., M.Sc., M.B., Ch.B., F.R.S. | The work of the Royal Naval Personnel Research Committee |
| E. A. Carmichael, C.B.E., M.B., Ch.B., F.R.C.P. | The work of the Military Personnel Research Committee |
| Sir Alan Drury, C.B.E., M.D., F.R.C.P., F.R.S. | Traumatic shock |
| Sir Alan Drury, C.B.E., M.D., F.R.C.P. and J. F. Loutit, D.M., M.R.C.P. | Blood transfusion, blood grouping and blood products |
| Professor L. J. Witts, M.D., F.R.C.P. | (1) Infective hepatitis and serum jaundice<br>(2) The work of the Therapeutic Requirements Committee |
| Professor H. P. Himsworth, M.D., F.R.C.P. | (1) The work of the Food Rationing (Special Diets) Advisory Committee<br>(2) The work of the Protein Requirements Committee |

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|---|---|
| G. S. Wilson, M.D., F.R.C.P., D.P.H. | The work of the Emergency Public Health Laboratory Service |
| Professor P. A. Buxton, C.M.G., M.R.C.S., L.R.C.P., F.R.S. and J. R. Busvine, D.Sc., Ph.D. | Medical entomology |
| Professor Sir Howard Florey, M.D., F.R.C.P., F.R.S. | The development of penicillin |
| Professor R. V. Christie, D.Sc., M.D., F.R.C.P. | The work of the Penicillin Clinical Trials Committee |

Thanks are due to Miss E. Cozens, of the Headquarters staff of the Medical Research Council, and Miss J. R. Taylor, B.A., Librarian of the National Institute for Medical Research, for their help in checking the references to publications.

The advice of Miss E. M. M. Hume, M.A., in regard to the preparation of the list of publications appended to Chapter 5 is gratefully acknowledged.

# CHAPTER 1

# ORGANISATION

THE term 'medical research' as applied to war problems covers work on a remarkable variety of subjects. In war-time the main objective of medical science is to conserve the effective manpower of the nation at the highest possible level; it follows, therefore, that medical research under war conditions is primarily concerned with problems bearing directly upon the prevention of disease and malnutrition among the Fighting Services and the civilian population, and upon the rapid restoration to health of the wounded and the sick. During the Second World War its scope came to be greatly extended so as to include the study of all factors which might affect the mental or physical welfare and efficiency of persons engaged in duties in any way connected with the conduct of the war.

The fulfilment of these manifold requirements entailed the diversion to the war effort of the great majority of the existing resources for medical research, the co-ordination of relevant activities in Government, academic and commercial research laboratories, the initiation of new inquiries to deal with special problems as they arose, and the recruitment and training of specialist workers in numbers sufficient to meet the expected demands for future expansion.

## The Role of the Medical Research Council

Administration of the funds provided yearly by Parliament for the promotion of medical research in Great Britain has been the function of the Medical Research Council ever since that body was established, under a Committee of the Privy Council, in 1920, in succession to the Medical Research Committee under the National Health Insurance Joint Committee. It was natural, therefore, that to the Council fell the predominant share of the huge task of organising and co-ordinating the research efforts of medical scientists in relation to the national needs in war. Even before the outbreak of hostilities, requests had been received by the Council from the Fighting Services and from civil departments for assistance in the application of scientific knowledge to the requirements of the war machine, and these demands increased greatly in number and frequency after the war started. It is interesting to recall, in this connection, that the Council's predecessors, the Medical Research Committee, had begun work in 1913, just in time to give valuable co-operation to the Army Medical Department and the civil authorities in dealing with urgent health problems encountered during the War of 1914–18.

In planning and carrying out their programme of investigations during the war, the Medical Research Council had the help of a very large number of expert technical committees, which they had appointed to advise on the promotion of researches in particular branches of medical science. Some of these committees antedated the war, whilst others were set up between September 1939 and August 1945 to meet special developments in the military situation. Among the subjects studied intensively by war-time committees of the Council were wounds and burns, gas gangrene, traumatic shock, brain and nerve injuries, malaria, the typhus fevers, infective hepatitis, tuberculosis and its detection by mass radiography, blood transfusion, the care of the shipwrecked, the clinical uses of penicillin and the various aspects of nutritional science bearing upon the feeding of a nation at war. Many of these committees owed their origin to requests by the Fighting Services or by Government Departments for advice on urgent problems, and they included in their membership representatives of the Fighting Services and of the Departments chiefly concerned. Standing committees of the Council which already by 1939 had accumulated a substantial body of scientific data, capable of immediate application in furtherance of the national effort, included the Accessory Food Factors Committee (appointed jointly with the Lister Institute of Preventive Medicine) and the Industrial Health Research Board. The Board's history is of special interest, for it was the direct descendant of the Health of Munition Workers Committee, set up by the Government at a critical stage of the War of 1914–18, to study working conditions in ordnance factories; that committee's views on the maximum hours of work for men and women in industry which were compatible with good health and sustained output were fully endorsed in researches carried out for the Council in the Second World War. A list of those who served upon the various war-time committees of the Medical Research Council is given in Appendix I.

### RESEARCH ON THE HEALTH AND EFFICIENCY OF MEMBERS OF THE FIGHTING SERVICES

The Council assisted the Admiralty, the War Office and the Air Ministry in solving many problems affecting the well-being and efficiency of members of the three Fighting Services in the Second World War. A Flying Personnel Research Committee had been established as a committee of the Air Ministry in January 1939, with Sir Edward Mellanby, the Secretary of the Medical Research Council, as its Chairman. Subsequently, in 1941 and 1942, a Military Personnel Research Committee and a Royal Naval Personnel Research Committee were appointed by the Council at the request of the War Office and the Admiralty respectively. Accounts of the origin, constitution and work of these committees are given in Chapter 2.

A large part of the programme of the personnel research committees can be grouped under the general heading of 'human engineering'; this type of study has been defined briefly as 'fitting the machine to the man and the man to the machine', and it has obvious applications not only to Service needs but also to industrial welfare and productivity.

### RESEARCH ON GENERAL PROBLEMS OF HEALTH AND DISEASE AND ON THE PREVENTION AND TREATMENT OF INJURIES

In Chapters 3–9 are given accounts of the investigations promoted or assisted by the Medical Research Council and other bodies on the treatment of wounds and injuries of different kinds, on infectious and other diseases which were important during the war, on nutritional and public health problems, on chemotherapy (including the development of penicillin as a therapeutic agent), on industrial health and hygiene, and on certain aspects of biochemistry, including the chemistry of penicillin; many of these studies were directed or co-ordinated by special committees, as has already been indicated. Where work on a particular problem was promoted wholly or in large measure by bodies other than the Medical Research Council, this is usually specifically mentioned in the text. Certain investigations made by independent workers, chiefly medical officers in the Fighting Services or members of the teaching staffs of universities, are also dealt with in these chapters. Chapter 10 gives a brief account of researches on methods of protection against war gases, which were mainly the responsibility of the Ministry of Supply, and Chapter 11 deals mainly with work promoted by the Ministry of Home Security on the biological effects of explosions, with special reference to problems of civil defence against air attacks; studies of the nature and treatment of the injuries due to underwater blast are also reviewed in Chapter 11.

### WARTIME RESEARCHES IN M.R.C. AND OTHER ESTABLISHMENTS AT HOME AND BY SPECIAL UNITS SENT ABROAD

The researches sponsored by the Medical Research Council during the war were carried out sometimes by specially appointed teams of investigators, but more often by members of the Council's scientific staff, working in the Council's own research establishments or elsewhere, by grant-aided or voluntary workers in university departments, or by members of the Fighting Services. In addition, much of the programme of the National Institute for Medical Research and of the Council's other pre-war research establishments was orientated towards war problems, whilst various new research units were started in the United Kingdom on either a permanent or a temporary basis; a temporary establishment of an unusual kind was the Physiological Research Laboratory, set up by the Council in 1940 at the Armoured Fighting Vehicle Training School, Lulworth, Dorset, in relation to the

programme of the Military Personnel Research Committee. Later in the war the Council, by arrangement with the Army authorities, despatched a number of mobile research units oversea to investigate particular problems in the field; among these were two research teams on traumatic shock, which worked in Italy and North-west Europe respectively, and the Scrub Typhus Commission, which investigated that disease in Burma and Assam. A British Army Typhus Research Team, including nominees of the Council, carried out clinical and pathological investigations on louse-borne typhus in North Africa and Italy in 1943–4.

At the National Institute for Medical Research, directed by Sir Henry Dale until October 1942 and thereafter by Dr. (now Sir) Charles Harington, influenza, malaria, the typhus fevers, and gas gangrene were among the diseases intensively studied in the laboratory, and important research was done on problems of air hygiene (in relation to the control both of wound infection and of the spread of epidemics among crowded communities in air-raid shelters), as well as on the physiological effects of special stresses to which Service personnel might be subjected; the investigations under the last heading were co-ordinated by Dr. G. L. Brown, of the Council's staff, who was Secretary of the Royal Naval Personnel Research Committee.* War-time studies in the Department of Clinical Research, University College Hospital Medical School, London, included work on injuries due to cold by the late Sir Thomas Lewis, who had directed the Department since its inception in 1919 and continued to do so until his death in March 1945; other investigations in the Department related to problems of traumatic shock. This was also the predominant war-time study of the Council's Clinical Research Unit at Guy's Hospital under the direction of Dr. R. T. Grant, while their Neurological Research Unit under Dr. E. A. Carmichael, at the National Hospital for Nervous Diseases, London, was during the war chiefly occupied with problems of environmental physiology studied on behalf of the Fighting Services; a substantial part of the laboratory research programme of the Royal Naval Personnel Research Committee was carried out in this Unit, where special 'climatic chambers' for examining the effects of hot and humid environments upon working efficiency were temporarily installed by the Admiralty; various investigations for the Flying Personnel Research Committee and the Military Personnel Research Committee were also made here, and Dr. Carmichael served as Secretary of the latter body. Accounts of important war-time researches in other pre-war establishments of the Council, or by individual members of their scientific staff, will be found in later chapters of this volume.

New establishments set up by the Council between 1939 and 1945, initially to deal with war problems, included a Burns Research Unit at

* From January 1944 Dr. Brown shared the secretarial duties with Surgeon Lieutenant Commander F. P. Ellis, R.N., who was appointed Naval Medical Secretary.

Glasgow and subsequently at Birmingham, and a Wound Infection Research Unit at Birmingham. The Department for Research in Industrial Medicine at the London Hospital was established primarily to study problems of industrial toxicology in factories engaged in war production, though its functions are obviously applicable to peace-time industry as well. The Applied Psychology Research Unit, set up in the Psychological Laboratory at Cambridge in 1944, likewise had its origin in war-time needs, though research in the Laboratory had been assisted by the Council for many years beforehand.

### EXECUTIVE FUNCTIONS UNDERTAKEN BY THE M.R.C. ON BEHALF OF GOVERNMENT DEPARTMENTS

Throughout the war period the Medical Research Council co-operated with various administrative Government Departments on matters of common interest. Co-operation with the Ministry of Health was particularly close and, in addition to arranging investigations of many health problems referred by the Ministry for advice, the Council undertook some important executive functions, the cost of which was borne on the Ministry's vote. These included the organisation and direction of an Emergency Public Health Laboratory Service for England and Wales, the establishment, staffing and equipment of four depots in the Home Counties for the collection and storage of blood for the transfusion treatment of air-raid casualties in the Greater London area, and the accumulation of stocks of various immunological agents (vaccines and sera) in adequate quantities for emergency needs. Another war-time task of the Council was to advise the Central Medical War Committee and the Ministry of Labour and National Service on the allocation of pathologists and pathological laboratory technicians to emergency duties; the Council maintained a register of workers of both kinds, and were thus able to ensure that their services and skills were used to the best advantage; arrangements were also made for the recruitment and training of new workers in pathology to meet the demands of the Fighting Services and the civilian health services during the war.

Apart from the setting up of the London blood supply depots, these executive duties entrusted to the Council in relation to the war emergency had a common origin in requests made by Government before the war for advice on the steps which should be taken to counter the risk of bacteriological warfare against this country—a risk which fortunately did not materialise in the War of 1939–45. As long ago as 1934, the Secretary of the Council had been consulted by the Government about possible dangers under this heading, and it was as a result of the advice given then and subsequently that the Council were made responsible for carrying out some of the precautionary measures deemed necessary. In the first place it was decided to build up reserves (and production potential) of various vaccines and antitoxins which might be required for

combating outbreaks of infectious disease, possibly of kinds not ordinarily occurring; in the event, however, the larger part of this problem was concerned with the supply of antitoxins for the more ordinary medical purposes of preventing tetanus and gas gangrene in the wounded. In the second place, it was considered that Great Britain was inadequately provided with laboratory facilities for the diagnosis and investigation of infectious diseases, and that a network of special public health laboratories, integrated into one service, should be organised to make good the deficiency; in this case also, bacteriological warfare was not the only danger in view, as there was at least as great a risk of natural epidemics occurring on a large scale, as a result of possible mass movements of the population and the partial breakdown of normal sanitary services under aerial bombardment. In the third place, it became clear that for this and other purposes there would, in the event of war, be exceptionally heavy demand for trained pathologists and skilled laboratory technicians, so that steps were necessary to ensure the most effective use of these categories of technical man-power.

In the field of blood transfusion the Council's executive responsibilities were at first limited to the organisation of supplies of stored blood for the resuscitation of air-raid casualties in the Greater London area, through the establishment of the four depots already mentioned, with ancillary arrangements for the provision of apparatus and of blood-grouping sera. They were, however, able also to give considerable assistance to the Fighting Services, and to co-operate with the civilian blood transfusion services subsequently set up by the Health Departments to cover the needs of the United Kingdom as a whole. As the war progressed, the Council further became responsible for developments made possible by the introduction of technical processes for preserving plasma and sera in dried form. Full accounts of the organisation of the Emergency Public Health Laboratory Service and of the Emergency Blood Transfusion Services, of which the London Blood Supply Depots were an integral part, are given in the Civilian Health and Medical Services and the Emergency Medical Services volumes of this History, and need not be repeated here. Much valuable research was, however, carried out by the staffs of these organisations, and that suitably finds place in this volume, as do the research aspects of the supply of vaccines and antitoxins (see Chapters 3 and 6). For accounts of the working of the Register of Pathologists and Laboratory Technicians, reference may be made to the Council's Reports for 1938–9 and 1939–45.

It is appropriate to mention here that the Emergency Public Health Laboratory Service proved so very successful in dealing with outbreaks of infectious disease and of bacterial food poisoning during the war that a Public Health Laboratory Service, on a similar but greatly expanded basis, has been maintained since the war ended. Statutory

authority for the Service was provided in the National Health Service Act of 1946.

## The Scientific Advisory and Scientific Food Policy Committees of the War Cabinet

Application of the resources of the Medical Research Council to a great variety of war-time tasks was assisted by the appointment of Sir Edward Mellanby, the Council's Secretary, to be a member of the Scientific Advisory Committee of the War Cabinet. This body, set up in October 1940, under the Chairmanship of Lord Hankey, also included in its membership the Secretaries of the Department of Scientific and Industrial Research and the Agricultural Research Council, as well as the President and two Secretaries of the Royal Society. Its terms of reference were to advise the Government on scientific problems referred to it, to assist in the selection of individuals for particular lines of inquiry or for service on special committees, and to bring to the notice of the Government any new scientific or technical development which might be of importance to the war effort. A Scientific Food Policy Committee of the War Cabinet had been set up, under the chairmanship of the President of the Royal Society, in May 1940. This was concerned chiefly with the application of scientific knowledge of nutrition to the problems of feeding a nation at war. It reported to the War Cabinet on food policy, and its work, which was almost completed by the end of 1941, had an important bearing on the subsequent policy of the Ministry of Food in regard to food imports, distribution and rationing. Sir Edward Mellanby served also on the Scientific Food Policy Committee and Dr. B. S. Platt, of the staff of the Medical Research Council, was one of its Secretaries—an arrangement both appropriate and useful, since research workers for the Council had been responsible for much of the fundamental work on which the committee's recommendations were based, and the Council's expert committees in the field of nutrition were able to arrange many of the necessary short-term studies of dietetic problems rendered urgent by the war situation. The Accessory Food Factors Committee did valuable work in this way (see Chapter 5). Another expert committee of the Council—appointed in 1940 at the request of the Ministry of Food, the Ministry of Health and the Department of Health for Scotland—has had the unenviable but very necessary task of advising on the modifications of the ordinary civilian rations which should be allowed for invalids requiring special diets; its work, also, is described in Chapter 5.

## Information and Liaison: Co-operation with Allied Countries

An important problem affecting the organisation of medical research activities during the war was that of securing a rapid and effective

exchange of scientific information between workers in the United Kingdom and those in other parts of the British Commonwealth and in Allied countries. Such a service was specially necessary in view of interruptions to the free international flow of scientific literature at this time. Information regarding much of the original work published both in Allied and enemy countries during the war years was made available through the medium of the *Bulletin of War Medicine*, a periodical consisting both of abstracts and review articles, which the Medical Research Council produced from September 1940 till August 1946, with the generous and invaluable co-operation of the Bureau of Hygiene and Tropical Diseases. Under war conditions, however, the initial publication of research results was often delayed by printing difficulties and the paper shortage in Great Britain or by other factors. A system providing for an exchange and dissemination of unpublished documents was therefore developed, and this was supplemented wherever possible by personal contacts.

In the U.S.A. the functions performed in Great Britain by the Medical Research Council were undertaken by the Committee on Medical Research of the Office of Scientific Research and Development (O.S.R.D.), which was established in June 1941. This body invited Sir Henry Dale, then President of the Royal Society and a member of the Scientific Advisory Committee of the British War Cabinet, to visit the United States and to assist in the formulation of its programme. He paid this visit in January 1942, accompanied by Professor E. D. Adrian. A medical liaison office of O.S.R.D. was set up in London and was maintained until 1945. Representatives of the Dominions, the U.S.A. and other Allied nations attended meetings of the scientific committees of the Medical Research Council in the United Kingdom; they also visited research laboratories and discussed matters of common interest not only with the investigators concerned but also with civilian administrative officers and with those of the Fighting Services. The information and impressions collected by U.S. liaison officers were transmitted to the Committee on Medical Research in Washington, which in turn made available to British colleagues the reports of American investigators. The Medical Research Council maintained their own liaison officers in the British Commonwealth Scientific Office in Washington, who transmitted to Britain information gleaned from the U.S. and Canada, and amplified and interpreted the reports of British work to the American and Canadian authorities. There was also close liaison between the National Research Council of Canada and the U.S. Committee on Medical Research.

Numerous short-term scientific visits to Allied countries were paid by British workers at different periods of the war; among these may be mentioned the visits of Professor H. W. (later Sir Howard) Florey and Dr. N. G. Heatley to the U.S.A. in 1940, and of Professor Florey and

Dr. A. G. Sanders to the U.S.S.R. in 1944. In 1943 a party of British, Canadian and American surgeons, including Sir Ernest Rock Carling as representative of the Medical Research Council, paid a goodwill visit to Moscow.

## Some Outstanding Achievements of Medical Research during the War

The mobilisation of the medical research activities of the Allied nations as an integrated component of the war machine affords a striking example of wise planning and wholehearted co-operation on the part of investigators and administrators alike at a time when all were working for the common good. As a result of this cumulative effort, important advances were made in many branches of medical science. The most impressive of these was undoubtedly the introduction of penicillin as a therapeutic agent, with its dramatic effect in the control of wound infection and many other diseases, though the development of synthetic drugs and insecticides for the prophylaxis and control of malaria and other insect-borne infections probably exerted an even greater immediate influence on the course of military operations. By the end of the war, malaria, typhus, dysentery, pneumonia and the venereal diseases, which in previous wars had proved a serious drain on man-power, had ceased to be problems of major military significance. The results achieved by the intensive study of nutritional and climatological problems, of traumatic shock, and of blood transfusion, though less spectacular, were also of great practical importance. Nor—in a more specialised field—should mention be omitted of the biochemical work at Oxford, which led to the development of 2:3-dimercaptopropanol ('British Antilewisite' or BAL) as an effective antidote to lewisite gas (see Chapter 10); although this did not need to be used for its primary purpose during the war, it has since been shown to have value in the treatment of various forms of poisoning.

While research into the fundamental problems of medical science was necessarily impeded by the war, the work on BAL mentioned above was only one of the many instances of practical applications of fundamental work done previously being accelerated to meet the special requirements of the times. The destructive action of penicillin on certain pathogenic bacteria had been demonstrated by Fleming in London as long ago as 1929, but the work of Florey and others at Oxford which led to the development of penicillin as a practical remedy, though started as an academic problem in 1939, was expanded rapidly to meet war-time needs once the high curative potentialities of the drug had been demonstrated; furthermore, the joint Anglo-American work on the chemistry of penicillin (see Chapter 11), and the arrangements under which American manufacturers successfully undertook large-scale production of the drug at a time when manufacturing resources in Great Britain were

mainly diverted to making munitions, were remarkable examples of a kind of international co-operation which, though very effective under war conditions, is hardly possible in peace.

The researches which resulted in the production of the first synthetic anti-malarial drugs, plasmoquine and atebrin, owed their origin to the fact that Germany was cut off from all sources of quinine in the War of 1914–18. Similarly, the immense volume of research which achieved such notable advances in the chemotherapy of malaria during the War of 1939–45 was undertaken because the Allies in their turn were deprived of quinine supplies when Indonesia fell to the Japanese. The development of various new insecticides and insect repellents based on studies carried out both in Great Britain and in the U.S.A.—following, in the case of D.D.T., an important lead from Switzerland—also owed its origin to the stimulus of war.

Although the impact of the Second World War on the progress of civilisation was in so many respects disastrous, the achievements of medical research during that period have already exerted a beneficial effect on civilian populations in many parts of the world, and there can be no doubt that intensive cultivation under more normal conditions of the new fields of scientific discovery then revealed will bring about developments of even greater value in the future.

# CHAPTER 2

# THE SAFETY AND EFFICIENCY OF THE FIGHTING MAN

THE investigations outlined in this chapter were of the types now generally described as 'Services Personnel Research'. This term connotes the study, by physiological and psychological methods, of the best means of increasing the fighting efficiency, safety and comfort of sailors, soldiers, and aviators under varying environmental conditions, and of adapting ships, fighting vehicles, aircraft, and weapons to the comfort and convenience of those called upon to operate them. It includes studies relating to the different types of ration issued to troops detailed for general or specialised duties; to the various types of clothing suited to service under tropical or arctic conditions; to the standards of vision, hearing, and other qualities required for particular tasks; and to the design of weapons and equipment with due regard to human capabilities and limitations.

In the realm of aviation, important physiological researches were undertaken during the First World War, notably in regard to oxygen requirements at high altitudes, and since that time Service departments have shown an increasing tendency to invoke the co-operation of research workers in the biological sciences in solving the many and varied problems in which the human factor is involved. During the period between the two world wars, the help and advice of the Medical Research Council were sought on a number of occasions by the Admiralty, the War Office and the Air Ministry.

As examples of *ad hoc* investigations arranged by the Council for the Fighting Services before 1939 may be cited the study of colour vision requirements in the Royal Navy, on which a report was published in 1933, an inquiry into the nutritional values of canned Army rations which began in 1937 and is described below, and a series of experiments on vocational selection tests for special duties in the Fighting Services which were carried out by workers under the Council's Industrial Health Research Board. In many other directions, researches planned before the war with primary reference to industry found useful application under war conditions to problems of Service personnel and equipment. The converse also applies, and numerous research techniques developed during the war to solve urgent Service problems have since been adapted to the solution of problems of industrial welfare and productivity.

During the Second World War, the manner and scope of personnel research were developed by the appointment of special committees of

Service representatives and civilian scientists to plan and direct it on a vastly expanded scale, and by the setting up of a number of new establishments for its intensive prosecution. The first combined Service and civilian committee appointed in Britain specifically to direct researches on physiological and psychological problems of Service personnel was the Flying Personnel Research Committee, set up nine months before the outbreak of war. Although this was a committee of the Air Ministry, the Secretary of the Medical Research Council served as its first Chairman and a substantial part of its war-time research programme was entrusted to members of the Council's staff. In 1941 and 1942 similar committees were appointed by the Medical Research Council, at the request of the War Office and the Admiralty, respectively, to direct programmes of research on problems affecting the Army and the Royal Navy. In addition, before the Royal Naval Personnel Research Committee was appointed, a special Committee on the Care of Shipwrecked Personnel had been established by the Council by request of the Admiralty; the Royal Naval Personnel Committee, with its much wider terms of reference, was a direct successor to this earlier committee, which had been appointed to investigate urgent problems arising from the intensive submarine warfare directed against this country.

## Work for the Royal Navy

### THE ROYAL NAVAL PERSONNEL RESEARCH COMMITTEE AND ITS SUB-COMMITTEES

The Royal Naval Personnel Research Committee began work in November 1942. The first investigation to be undertaken related to conditions in Coastal Force craft. Representatives of the committee visited coastal force bases and a number of recommendations were made for the improvement of clothing and of living conditions, particularly in regard to the reduction of condensation and the elimination of noise. Arrangements were also made for a naval medical officer to record observations on climatic and other conditions obtaining during passage on a northern convoy proceeding to Murmansk and Iceland. The success of this method of collecting accurate scientific information led subsequently to further expeditions by medical observers to study problems of naval warfare under extremes of climate (Critchley, 1945, 1947).

### UNDERWATER PHYSIOLOGY

Early in 1943, developments were in progress in underwater warfare which led eventually to an extended use of the human torpedo and the X craft submarine, and entailed the employment of divers on a large scale for reconnaissance, for clearance of beach obstructions, and for the recovery of enemy mines. The Admiralty wished for a considerable

extension of physiological research on diving and cognate matters, and requested the Royal Naval Personnel Research Committee to undertake its co-ordination. This led to the formation of the Sub-committee on Underwater Physiology, which contributed some of the most notable material with which the committee was concerned. Part of the sub-committee's programme was carried out by the Admiralty Experimental Diving Unit and part at the National Institute for Medical Research. In addition, a recommendation by the sub-committee resulted in the establishment of the Royal Naval Physiological Laboratory. Three separate laboratories were thus involved in the difficult and dangerous studies of diving problems, and the committee sponsored a number of sea trials of diving gear, which also involved the Interservices Research Bureau, then engaged in developing such gear for other purposes (Gay French, 1946; Dickens, 1946; Donald, 1947; Paton and Sand, 1947; Taylor, 1949).

A later development of the underwater studies was research on diving equipment for use in tropical seas. The sub-committee also fostered the development of air-purifying gear for submarines and arranged instructional courses for the commanding officers of these vessels. Sea trials were carried out in submarines under war conditions, and data on atmospheric conditions were collected.

### PROBLEMS OF NAVAL GUNNERY

In February 1943, as the result of a request from the Director of Naval Ordnance, a Gunnery Sub-committee was set up. Its initial studies had the object of improving the conditions of work for men under exposed conditions in Director Control Towers, but it soon became clear that useful advice could also be given in regard to the general design of gunnery equipment of many types. A problem of major interest was that of the comfort and efficiency of the seated operator working sights and hand-wheels, since there was a natural tendency on the part of designers to assemble components in a manner giving the maximum of constructional simplicity, which too often made little allowance for the human factor. Valuable work on this and related subjects was done in the Department of Human Anatomy at Oxford University (Le Gros Clark, 1946; Darcus and Weddell, 1947; Weddell and Darcus, 1947). Another aspect of the problem of the human operator was met when measurements were made of the energy output of turret crews. With the inevitable speeding up of naval warfare, it became apparent that restriction of the rate of fire depended on limitations not so much of the mechanical equipment as of the men who had to feed it. Re-design of equipment, and a re-allocation of tasks, did much to counteract this difficulty, and, together with careful regulation of environmental temperature and humidity, reduced the likelihood of human breakdown.

HABITABILITY OF SHIPS

The realisation in the spring of 1943 that intensive naval operations in tropical waters were imminent impelled the committee to recommend the despatch of two observers to the Mediterranean, Levant and Eastern Fleet. Their reports made it clear that the atmospheric conditions in H.M. ships were not conducive to a maintained high level of efficiency in their complement. At the same time, the Admiralty asked the committee to undertake research work with a view to determining the standards of habitability in ships which would be consistent with maximum efficiency. This request led to the formation of a special Habitability Sub-committee, which initiated investigations on a considerable scale. It was essential in the first place to secure quantitative data on the environmental conditions in H.M. ships under war conditions, with the additional handicaps imposed by the necessity of darkening ship, by swollen complements, and by rigorous damage control measures, all of which affect adversely the air conditions on board. With this end in view, the committee despatched a mission to the Eastern Fleet, including two Naval medical officers and a Naval constructor, together with technical assistants and the necessary apparatus. The collaboration of a naval constructor with medical men proved exceptionally valuable, and the mission, besides producing detailed information on conditions obtaining in the Fleet, were able to suggest material improvements in the standards of living in most of the ships visited (Ellis, 1947, 1948).

At the same period steps were taken to initiate experimental investigations in Great Britain, and the Admiralty equipped two climatic chambers in the National Hospital for Nervous Diseases, London, and one in the Psychological Laboratory at Cambridge University. Studies were made of the effects of hot and humid environments on naval ratings engaged on tasks similar to those which they would be called upon to perform in ships cruising and in action under tropical conditions (Ladell, 1945, 1947, 1948, 1949; Mackworth, 1946, 1947, 1950; Weiner, 1945, 1946; Weiner and Hutchinson, 1945). At an early stage it became clear that the levels of temperature, humidity, and air movement suggested by the sub-committee as the limits permissible on *a priori* grounds were in fact very near the figures at which fighting efficiency would suffer, and the observations of the Eastern Fleet Mission showed that such temperatures were frequently exceeded in living compartments, and in compartments where the work done was vital to the ship's fighting organisation. Steps were immediately taken by the Admiralty to improve this state of affairs, in the first place by temporary expedients and secondly by making alterations in the design of ships under construction and planned. A handbook on environmental warmth and its measurement, together with a series of large-scale charts for making the necessary

corrections, was prepared (Bedford, 1946), and was adopted by the Admiralty for use in H.M. ships. It was also decided to supplement these investigations by a study of tropical conditions in the field, and for this purpose a planning mission was despatched to the Far East to organise a Tropical Research Unit; this Unit was established, after the end of hostilities, at Singapore.

An investigation of a different kind, sponsored by the Habitability Sub-committee, related to the bacterial content of the air in warships, from the point of view of the risks of the spread of epidemics among the ship's company (Ellis and Raymond, 1948).

### PROTECTIVE CLOTHING

The Clothing Sub-committee of the Royal Naval Personnel Research Committee was appointed primarily to consider the problem of clothing for gunnery ratings in exposed positions. It worked under the inevitable handicap imposed by wartime shortage of supplies, and its programme was restricted by lack of trained observers in sufficient numbers to undertake effective field trials. Since an intimate relationship exists between a man's clothing and his tolerance for climatic extremes, close association was maintained with the Habitability Sub-committee in regard to such questions as the most suitable clothing for ratings manning the lower quarters of turrets. The Clothing Sub-Committee was able to design and test anti-flash gear, capable of providing adequate protection without imposing too great a load on the wearer's heat-regulating mechanism, and to devise an action rig for tropical wear. It also gave advice as to the type of clothing suitable for service in the Arctic, and sent an observer to attend the elaborate cold weather trials carried out in Canada by the Dominion Armed Forces. Other problems studied were those of blast protection for gunners, and the design and testing of body armour and flotation devices for Coastal Forces and other branches of the Service.

### OTHER ACTIVITIES OF THE ROYAL NAVAL PERSONNEL RESEARCH COMMITTEE

Among many additional questions examined by the Royal Naval Personnel Research Committee with the aid of special sub-committees or groups of investigators were those of auditory training for anti-submarine listening and the testing of colour vision and vision at night. In general it may be said that the committee's effectiveness in so many fields of inquiry both inside and outside orthodox medicine has been due to the happy collaboration established between the executive Service officers, the officers of the Royal Naval Medical Service, and the Service and civilian scientists concerned with its programme. A list of the war-time members of the Committee and its principal sub-committees will be found in Appendix I.

### THE CARE OF THE SHIPWRECKED

A Committee on the Care of Shipwrecked Personnel (Appendix I) was established by the Medical Research Council at the request of the Admiralty in 1941. Its members included nominees of the Air Ministry and of the Ministry of War Transport as well as naval representatives, since its terms of reference extended to the hazards of aircrew brought down into the sea and of merchant seamen exposed to the dangers of unrestricted submarine, surface, and aerial warfare. Special attention was given to the choice of rations for issue in ships' lifeboats. It was realised from the outset that the greatest single factor in the preservation of life at sea after shipwreck is an adequate supply of drinking water; water is relatively much more significant than food in these circumstances, although a careful choice of suitable food rations to sustain physique and morale is also important (Critchley, 1943). A number of trials were made in human volunteers to determine the minimum daily intake of water necessary to maintain health, and to decide the most economical way in which water could be rationed in lifeboats to secure maximum survival (Black, 1945; Black, McCance and Young, 1942, 1944; Ladell, 1943, 1947; McCance, 1945; McCance, Young and Black, 1944). The recommendations of the Committee in regard to water and food rations, and to many other important matters affecting the shipwrecked, were incorporated in a memorandum entitled 'A Guide to the Preservation of Life at Sea after Shipwreck' (Medical Research Council, 1943). (See also Medicine and Pathology Volume, Chapter 11.)

Two special hazards of the shipwrecked—namely, immersion limb and injuries due to underwater explosions (underwater blast)—are discussed in Chapters 3 and 11 respectively below.

## Work for the Army

### THE VITAMIN CONTENT OF ARMY RATIONS

In 1937, as a result of a request to the Medical Research Council from the War Office, an inquiry into the content and stability of vitamin C (ascorbic acid) in canned foodstuffs such as are used for field rations was begun by Dr. S. S. Zilva, of the Council's staff, working at the Lister Institute, London. By the outbreak of war, sufficient information had been gained to concentrate attention on the possibilities either of increasing the content of the natural vitamin by including suitable varieties of potatoes, lifted at the optimum time, or of selecting articles in the field ration for fortification with synthetic ascorbic acid.

It was found in a preliminary study, before the war, that the vitamin-C content of the meat and vegetable ration could be increased by including certain varieties of potatoes lifted early. Efforts, therefore, were

made to discover whether this held true in large-scale production, and also how the content of the vitamin might be affected by conditions of storage. Material from the base provision depots of 'Paiforce', and of the Middle East and West Africa Commands, was examined, as well as rations stored in the United Kingdom. The amount of the vitamin in the canned potatoes was shown generally to be satisfactory, especially if the canning had been done soon after lifting; no appreciable deterioration was noted after storage even in hot climates.

The suitability of jam and chocolate as media for enrichment with supplementary ascorbic acid was investigated. In the case of jam the fall in vitamin content was shown to be very small both during preparation under factory conditions and on storage: however, jam is an inconvenient vehicle for the administration of extra vitamin C in the field. Chocolate, on the other hand, suffered a significant loss of the synthetic vitamin after twelve months' storage, although the losses in preparation, or due to the high temperatures of tropical climates, were small. As a result of these experiments, it was reported to the Service authorities that although the large-scale enrichment of chocolate with ascorbic acid was not economically justifiable, this expedient might be useful on a limited scale in certain circumstances. It was successfully adopted during the Burma campaign.

Research on the vitamin content of Army rations also formed part of the pre-war and war-time programmes of the Dunn Nutritional Laboratory, Cambridge, directed by Dr. L. J. Harris. Special attention was given here to the content of vitamin $B_1$. It was found that the Army emergency ration, which for military reasons had to be packed in tins and thus subjected to heat treatment, was deficient in this vitamin. A wheatmeal biscuit, tested as a means of replacing the deficiency, was found ineffective, because the vitamin $B_1$ in it had been destroyed by the baking powder used in its manufacture; while a commercial yeast extract, also considered, was shown to lose much of its potency on storage. The remedy eventually devised was to substitute the less alkaline ammonium carbonate for the sodium bicarbonate in the baking powder, or better, to bake the biscuits with yeast instead of baking powder; biscuits made thus proved a reliable source of the vitamin, even after storage under adverse conditions in the tropics. It was also shown that a further substantial improvement in the vitamin-$B_1$ content of the biscuits could be brought about by substituting wholemeal flour for the less highly extracted wheatmeal flour.

Certain other Service dietaries, including the standard Naval ration for use afloat, were examined at the Laboratory, and suggestions were made for their improvement, these studies being combined with many other investigations into the nutritional values of different war-time foods as well as with researches into fundamental problems of nutrition. For a fuller account of the war-time work of the Laboratory, with the

names of those engaged in it, reference may be made to the Report of the Medical Research Council for 1939–45, pp. 291–303.

A number of general improvements in Service feeding arrangements were recommended as a result of surveys carried out, both before and during the war, by workers for the Medical Research Council at the request of the Service Departments.

### THE MILITARY PERSONNEL RESEARCH COMMITTEE AND ITS SUB-COMMITTEES

Field experience in the earlier months of the war, and particularly during the phase of active operations leading up to the evacuation from Dunkirk in 1940, brought to light many problems affecting the efficiency of the soldier in combat. The first problem of this nature to be referred to the Medical Research Council by the War Office was that of ear protection against battle noise. As a result of the close association then developed between the General Staff and members of the Council's scientific staff, the Army Council in September 1940 invited the Medical Research Council to advise also on forms of body protection, about which there was at this time considerable controversy. This request led to the appointment of a Body Protection Committee, on which representatives of the General Staff and of the Royal Army Medical Corps were invited to work with civilian scientists; the same committee was asked to report on the advisability of using vizors to protect the eyes in battle, and on the need to improve the design of steel helmets. In the following year the committee was enlarged and strengthened by further appointments, and its name was changed to that of the Military Personnel Research Committee. One of the committee's most important general recommendations was that expert advisers be attached to Army Headquarters in various theatres of war to obtain accurate scientific data regarding battle conditions and to report on relevant physiological problems. Scientists selected by the Medical Research Council were accordingly attached to Army Headquarters in Cairo, in India, and in the United Kingdom, with a directive from the Army Council giving them facilities for entering battle zones and reporting direct to the Army Council and the Medical Research Council on urgent matters. This was the first instance in which civilian scientists, with temporary commissioned rank, were attached to battle headquarters; the practice was subsequently developed on a wider basis, and from it were evolved the Operational Research Groups established in later years, which carried out many valuable investigations in the field.

In 1941, the General Staff sought help from the committee in regard to problems of defence against flame-throwers, and the Medical Research Council arranged for Dr. R. B. Bourdillon, of their staff, to co-operate with the Petroleum Warfare Board in work on this subject. By a series of experiments involving considerable personal risk he was able to

obtain data on the relative efficiency of various flame-throwing devices, and to suggest means of protection against them.

Many different lines of investigation were undertaken by the Military Personnel Research Committee, and as successive subjects for study developed, special sub-committees were appointed to deal with them. A list of the war-time members of the committee and its sub-committees is given in Appendix I. Some of the principal studies organised by these sub-committees are briefly reviewed below.

### SUB-COMMITTEE ON BODY ARMOUR AND STEEL HELMETS

From a study of casualties returned from Dunkirk, experiments with animals, and tests to determine the penetrability of different thicknesses of materials, a type of body armour was designed which was subjected to a field trial in North Africa, though it was not generally adopted. During this work important information was obtained as to the relative penetrating power of different bullets and weapons. The research was extended to include the design of protective armour for the crews of light anti-aircraft guns. Steel helmet design was considered and a new type was evolved; advice was also given regarding crash helmets for motor cyclists and parachute troops. At the request of the War Office, data were collected regarding the value of vizors for the protection of the eyes. After critically weighing their effects in impeding good vision against their potential advantages, the sub-committee advised against the wearing of vizors by troops in battle, and this recommendation was accepted by the Army Council.

### SUB-COMMITTEE ON CLOTHING

Some of the experiments relating to the design of clothing suitable for special troops were carried out at the London School of Hygiene and Tropical Medicine, others at the National Hospital for Nervous Diseases. Close co-operation was maintained with the Clothing Sub-committee of the Royal Naval Personnel Research Committee on matters of common interest. The relative merits of permanent and non-permanent waterproof finishes for textile fabrics were studied, and various improvements were suggested and adopted in respect of the clothing issued to Army Despatch Riders. In regard to the garments issued to anti-aircraft gunners, it was specified that these should be warm, water-repellent, flexible, strong, but not too bulky, and should permit men to sleep comfortably in their working clothes. The Wool Industries Research Association produced a double-pile woollen fabric which possessed high thermal insulation values and excellent water-shedding properties.

Various patterns of suits intended for use by the Royal Armoured Corps were tested in association with workers at the Physiological Research Laboratory set up by the Medical Research Council at the

Armoured Fighting Vehicle Training School, Lulworth (see below). A denim working overall and a tank oversuit were designed and models submitted for trial. As a result of these tests, and in the light of reports as to the supply situation of specially woven fabrics, a committee set up by the Quartermaster General approved revised specifications for clothing for tank crews; sufficient numbers of the new garments were available for the Normandy landing and subsequent phases of the campaign in Europe, where they proved very satisfactory.

At the request of the General Staff, the equipment designed for use in cold climates was studied in detail. The issue of this clothing was a matter of urgency, and the sub-committee reported that although it might be improved by certain modifications, the existing pattern was adequate for immediate needs. Through the medium of the sub-committee, scientists working in the field of cotton and woollen textiles were able to advise the War Office on methods of saving material during the manufacture of clothing, and of ensuring salvage and repair of clothes and boots to the best advantage.

### SUB-COMMITTEE ON WEAPONS (BIOLOGICAL ASSAY)

Studies were made as to the effects of blast produced by a variety of weapons upon personnel operating in confined spaces such as pill-boxes, armoured fighting vehicles, and buildings converted for defensive purposes. It was concluded that explosions occurring outside armoured fighting vehicles which did not cause any breach in the protective wall, entailed no significant danger from blast to men within them. Special trials with more formidable explosives showed that blast injuries incurred under these conditions were likely to be limited to ruptured ear drums, and damage due to displacement of the body; the risks of injury caused by fragments of armour plate would be much greater. Tests on concrete pill-boxes showed that open embrasures did not concentrate the blast waves upon the body of a gunner operating behind the embrasure. An assessment of the effects of certain types of grenades indicated that the danger to life from blast due to these weapons was negligible, while from other trials it was concluded that earphones gave a substantial degree of protection to the eardrums.

### ENTOMOLOGICAL SUB-COMMITTEE

One of the earliest activities of this sub-committee was to promote the investigation of insecticides against body lice. After preliminary trials in Great Britain, experimental work undertaken in the Middle East demonstrated the superiority of lauryl thiocyanate and certain proprietary thiocyanates (the lethanes) to the insecticides hitherto used for the purpose. New mosquito repellents were investigated in West Africa on behalf of the sub-committee, and apparatus for their application under field conditions was devised. The danger of mosquitoes

infested with certain diseases being conveyed to virgin territories by aircraft was brought to the attention of the authorities in Great Britain and in Allied countries, and recommendations were put forward for the more rigorous control of aircraft disinfestation. With the advent of D.D.T. the work of the sub-committee decreased, and it was eventually taken over by a committee of the Ministry of Supply (see Chapter 10).

### SUB-COMMITTEE ON AIRBORNE TROOPS AND ON MOTION SICKNESS

The problem of combating motion sickness, such as may occur in sea-going vessels, airborne gliders, and aircraft was a matter of joint concern to the three Fighting Services. In response to a request from the staff of Combined Operations for information on this subject, laboratories were equipped at the National Hospital for Nervous Diseases, for a study of the physiological mechanisms involved. By means of a swing apparatus, subjects prone and resistant to motion sickness were carefully studied; a finding of special interest was that motion sickness could not be produced in the absence of properly functioning aural labyrinths. Trials were made of various remedies for sea and air sickness, and the value of hyoscine for the purpose was demonstrated. By arrangement with the Admiralty and the War Office, field and sea trials were organised and attended by workers for the Medical Research Council (Holling, McArdle and Trotter, 1944); these trials confirmed the value of hyoscine for the prevention of motion sickness; similar tests carried out in gliders, with the co-operation of the Flying Personnel Research Committee of the Air Ministry, also showed the value of this drug. Subsequent experience in the British and United States Forces endorsed the conclusions submitted to the Service Departments on the basis of these and other tests.

### SUB-COMMITTEE ON VISION

This sub-committee worked in close liaison with the Vision Committee of the Flying Personnel Research Committee. An important part of their joint programme related to means of preserving the state of dark-adaptation necessary for night vision, while still permitting efficient map-reading at night; the need for special training in the use of night vision was urged. In association with members of the staff of the National Physical Laboratory, a series of experiments was arranged into the value of glare and dazzle as a defensive and offensive measure (Stiles, 1947). Much of the other work of this sub-committee came into the purview of the Sub-committee on Armoured Fighting Vehicles (see below).

### SUB-COMMITTEE ON ANALEPTIC SUBSTANCES

Investigations into the effects of administering analeptic drugs to R.A.F. personnel under different Service conditions were undertaken

as part of the programme of the Flying Personnel Research Committee (Davis, 1947). In response to a request from the War Office in 1941 for advice on the value of drugs of this type as a means of increasing the fighting efficiency of troops, a special sub-committee of the Military Personnel Research Committee was set up to investigate the matter and to plan any necessary experiments. The information at that time available was not sufficient to warrant the submission of recommendations regarding the uses of amphetamine ('Benzedrine') and related substances by Army personnel, and field trials were deemed essential. Observers were at first attached to British Army establishments during large-scale manoeuvres; but the inability to obtain satisfactory controls, or to establish adequate experimental conditions during routine manoeuvres, made it necessary for a special investigation to be undertaken for the sole purpose of evaluating this form of medication as a means of overcoming fatigue. With the co-operation of the Canadian Army authorities, a series of field exercises was planned, in which it was shown that a single dose of 5 mg. of amphetamine, or a 5 mg. dose repeated once, caused no appreciable alleviation of the fatigue induced as the result of long day and night marches, digging of trenches, and other military duties. Another series of trials showed that 10 to 15 mg. of amphetamine caused increased wakefulness in fatigued men, but that there were wide individual variations in the response to this drug and to the related analeptic 'Methedrine', limiting both their usefulness and their safety (Cuthbertson and Knox, 1947). It was concluded that drugs of this type should not be administered to troops without a preliminary test dose, but that these substances might be useful in helping tired men whose task was known to be terminating within four to five hours, or was of such a character that hope of survival was negligible except by a supreme effort. The War Office subsequently issued a directive on the permissible use of analeptics, which tallied closely with the recommendations of the sub-committee.

### SUB-COMMITTEE ON ACCIDENTS TO ARMY VEHICLES

A sub-committee set up to investigate the problem of preventing accidents to Army wheeled vehicles reviewed the methods used in the selection and training of drivers, and examined and analysed Army accident statistics. Recommendations were made to the War Office.

### SUB-COMMITTEE ON RATIONS

This sub-committee was appointed to carry out experiments on suitable forms of compact ration for issue to special troops, such as Commandos and airborne troops. Many of the novel features of the compact ration so devised were subsequently incorporated in an Army standard ration.

The experience gained by workers for the Medical Research Council who had volunteered to submit to conditions of water-deprivation such as might be encountered on ships' lifeboats adrift—as part of the research programme of the Committee on the Care of Shipwrecked Personnel (p. 16)—was later applied in a field inquiry, undertaken for the War Office, into the salt and water requirements of troops operating in tropical climates. Accounts of this study, which was carried out in Southern Iraq in the summer of 1943, have been published (Ladell, Waterlow and Hudson, 1944; Waterlow, 1947); it included interesting clinical observations upon the nature and prevention of the different types of heat effects encountered.

SUB-COMMITTEE ON ARMOURED FIGHTING VEHICLES

In October 1940, as a result of consultations with the Army Council and the Directorate of the Royal Tank Corps, the Medical Research Council established a special Physiological Research Laboratory at the Armoured Fighting Vehicle Training School, Lulworth, for the investigation of problems relating to the safety and efficiency of the crews of these vehicles. The first Director of the Laboratory (1941–2) was Dr. O. M. Solandt; he was succeeded, in turn, by Dr. G. L. Brown (for a short period), Professor I. de Burgh Daly (1942–5) and Dr. E. E. Pochin (1945). A list of the Service officers and civilian workers who shared in the research programme of the laboratory is given in the Report of the Medical Research Council for 1939–45.

Simultaneously with the establishment of the Laboratory, an Armoured Fighting Vehicles Sub-committee of the Military Personnel Research Committee was appointed, its membership including representatives of the appropriate departments of the War Office and the Ministry of Supply, as well as scientists nominated by the Council. The function of the sub-committee included the definition of problems for study, the promotion of interdepartmental co-operation, the assessment of results, and the transmission of recommendations to the Departments and Directorates concerned. The chief problems investigated are reviewed below.

*Fume Hazards.*—One of the earliest questions examined was the danger to health and efficiency arising from a concentration of toxic gases inside an armoured fighting vehicle (A.F.V.), resulting especially from the firing of Besa machine guns. Improved methods of ventilation were devised to counteract this danger, and a routine method of testing new types of A.F.V. and their weapons was agreed upon, as well as the maximum concentration of the noxious gases permissible. Ultimately a satisfactory ventilating system was evolved for each new type of A.F.V. produced during the war. As this hazard arose from fumes consequent on the firing of guns, investigations were carried out to determine the actual source of the fumes within the mechanism of the gun itself:

these led to proposals for alterations in the design of guns, and for improved methods of disposing of spent shell cases and cartridges. Fume hazards were also found to arise from ineffective disposal of exhaust gases. In sea-craft designed as tank landing ships, these hazards were very great, and practical trials showed that the crews of several vehicles carried in such craft had a dangerous level of carboxyhaemoglobin in their blood. This information was at once brought to the notice of the Admiralty, who accepted the need for making arrangements for the better disposal of exhaust fumes, and for a more rigorous and elaborate landing drill, in order to minimise the danger.

*Environmental Problems.*—Crews of A.F.Vs. operating in hot dry and hot wet climates are liable to be subjected to severe physiological strain owing to the increase of temperature and humidity within a vehicle. Studies were therefore undertaken to determine the effect on efficiency of wearing Army clothing (including gas-protective clothing) in environments similar to those obtaining in the North African Desert and the Far East. The work output of different members of a tank crew under conditions simulating battle was determined, such conditions being artificially produced in specially equipped laboratories at the National Hospital for Nervous Diseases and elsewhere; some aspects of this problem were studied at the National Physical Laboratory, by arrangement with the Department of Scientific and Industrial Research. It was established that under conditions corresponding to those obtaining in the period immediately preceding the monsoon, the heat and humidity within a tank might become almost intolerable, with consequent deterioration in efficiency. A form of 'personal ventilation', by means of specially designed clothing, was evolved; it was found satisfactory in practical tests, as well as being economical in space and weight of machinery. Improved ventilating systems were also investigated. Subsequently, the Ministry of Supply accepted recommendations for the design both of improved ventilation of vehicles and methods of 'personal ventilation' for the use of crews in the Far East war theatre.

*Vision.*—At an early stage it became clear that modern knowledge of lighting, and of the physiological mechanism of vision, could be effectively applied to increasing the fighting efficiency of A.F.V crews. The interior lighting of tanks at the beginning of the war was in many respects defective; some parts of the vehicles were insufficiently lit by day, and very much too brightly lit at night, interfering with the important function of dark adaptation. An improved lighting arrangement was designed and suitable fittings were prepared in consultation with supply firms. Measures were also suggested for the instruction of tank crews in the more effective use of night vision, and for this purpose a pamphlet written by the staff of the Lulworth Laboratory was accepted by the War Office as a training manual. As a result of this work, a member of the staff was requested by the Director of Military Training to study

methods of eye training and visual observations in use throughout all branches of the Army and to make proposals for their development. A report (unpublished) resulting from this study formed the basis for revision of the training programmes undertaken by the Camouflage Development and Training School.

One of the problems encountered was the dazzling of gunners by the muzzle flash of tank guns in failing light. On the basis of field experiments, the use of a simple shutter attached to the telescope was adopted, and the drill of firing was revised. In these experiments, the retinal area bleached by the flash was estimated; parallel observations were made on the duration of dazzle after seeing a flash from a 'point source', and on its relation to duration and brightness of the flash, as well as to the illumination, size and contrast of target. The data obtained were of value also to the Admiralty in relation to problems connected with the defence of merchant ships. As bigger guns were introduced, difficulties in observation of the fall of shot arose even in daylight, and investigations established that the causes of obscuration were multiple. The assessment of the relative significance of these various factors had important technical and operational implications.

A major problem in tank design was to provide adequate fields of visual observation for the crew without endangering their safety. This was especially necessary in the case of the commander, as it had been found that casualties among tank commanders were high, through their exposing their heads in order to obtain good all-round vision during battle when the optical devices supplied for the purpose proved inadequate. Members of the staff of the Laboratory devised means of overcoming the difficulty by arranging a sufficiently close grouping of periscopes in one part of a rotating cupola, so that good vision could be obtained in any direction required, though not over the entire range at once. The original conception of a ring of periscopes had emanated from the Royal Armoured Corps Experimental Wing, but the new design evolved in the Laboratory had the advantage that the area of battle would be in view from a single head position, without requiring constant head movement. The design was put into production early enough to allow of its being used at the Normandy landings, and the number of casualties to tank commanders was thereby reduced. Fields of view from other crew positions and from the tank as a whole were studied, and by alteration of design and placing of periscopes 'blind spots' were minimised.

During this work on problems of vision it became apparent that, in the design of certain optical instruments, allowance had not been made for optimum performance in dim light. Workers at Lulworth, in association with members of the Applied Psychology Research Unit at Cambridge, accordingly advocated an increase in the diameter of the 'exit pupil' of tank telescopes, and the 'blooming' of the lens surfaces.

The Admiralty Research Laboratory had shown that the illumination of telescope aiming marks at night caused some obstruction to vision. Calculations on the glare effect of graticules showed that the glare arose from a physical cause in the graticule plate, rather than from a physiological cause. As telescopes had to be usable both by day and by night, the thickness and display of graticule lines were matters of significance. The information elicited from experiments made at Lulworth on this subject was used in the specifications laid down for future telescopic sights.

Experiments on accuracy of aim were begun in 1943. A special point studied was the obscuration of targets by the graticule line, and the need for having no lines at the central point of aim. This work led, early in 1944, to a review of graticule design, following which the 'split cross' was introduced as the standard aiming mark in tank and anti-tank sighting.

The studies just described were related to current instrument design through an A.C.I.G.S. committee, formed to consider and co-ordinate sighting problems in general. This Tank and Anti-Tank Sighting Committee was soon afterwards resolved into separate committees on tank and on anti-tank sighting problems, respectively, on both of which members of the Medical Research Council staff at the Lulworth Laboratory were appointed to serve. Observations on tank and anti-tank gun sights soon indicated the relative importance of various sources of error in marksmanship. It was evident, however, that these factors required more careful analytical investigation, and from this point the experimental researches progressed in two directions: there was need, firstly, to give answers to specific problems raised by the Design Department, and secondly to initiate schemes of research into the physiological and psychological aspects of efficient gun-laying. Much of this work on gunnery gave insight into the general problem of the acquisition of accuracy in marksmanship, and some of the apparatus evolved was immediately applicable to training devices.

*Tank Driving.*—As the work of the Lulworth Laboratory began to influence tank design, increasing attention was paid to factors which tended to limit the full efficiency of the driver. Measurements of the work output of a tank crew showed that the driver was called upon to do more physiological work than any other member of the crew, except during brief periods when the loader was actually loading the main armament. The limiting factors in driving efficiency—physiological, anatomical and psychological—were studied and appropriate recommendations made (Hugh-Jones, 1947).

The inquiries briefly mentioned above not only had an important bearing on the future design of tanks, but also were closely integrated with the programme of the Royal Naval Personnel Research Committee on the design of gun turrets for the Navy. When the work on tank driving

was initiated, it was realised that in order to assess the correct design of seat and display of levers, anthropometric data would be required. A certain amount of relevant information had been collected by similar units in the U.S.A., but further measurements were found necessary, and in 1943 a survey of body measurements of Royal Armoured Corps personnel was carried out. The data obtained, which were subsequently applied in tank design, permitted a proper allowance of 'crew space', and the utilisation of this to the best advantage.

*Casualties among Tank Crews.*—In the open warfare of the Libyan Desert, fires in tanks were relatively common, and burns caused an important proportion of the injuries sustained by tank crews in battle. To reduce these, there was need not only for improved armour and anti-fire measures but also for better escape exits from the tanks. A quantitive study of the factors prolonging the time taken to get out of a tank was among the investigations undertaken co-operatively by expert observers in the field and at the Lulworth Laboratory. Lengthy and obstructed escape pathways, obstacles, badly designed hatches and the use of the same hatch by more than one member of the crew were found to be the main causes of delay. In subsequent observations, the minimum and economical size and shape of hatch for 90 per cent. of the tank crew 'population' were determined. The recommendations on hatch design eventually made found practical application in the newer models of tanks. Heavy hatch doors were spring-loaded, storage space was altered, and practice in rapid escape advised for the crews.

Impressed by the value of such studies, and realising that there was still a lack of adequate information regarding the causes and frequency of wounds in tank personnel, the Sub-committee on Armoured Fighting Vehicles recommended the despatch of special investigators to Normandy to collect relevant data in the field. The War Office supported the project, and R.A.M.C. observers chosen by the Medical Research Council were attached for this specific purpose to 21 Army Group. They found that a high proportion of the men became casualties when dismounted; they noted the frequency of casualties resulting from partial exposure of the body through a hatch, and the number associated with mechanical damage to the tank; they also analysed, where possible, the nature of the causative missile. In addition to the survey of casualties, a study of the site or sites of damage to the tank was undertaken.

In parallel with the field observations in Northern Europe, the causes of wounding in casualties among tank crews returned to hospitals in Great Britain were investigated. The high incidence of casualties among dismounted crews was confirmed; it was also found that the majority of injuries resulted from fragments, and that blast and displacement injuries were relatively unimportant. An analysis of the recovery rate of the patients showed that burns were much the least severe forms of

injury among the survivors who reached Britain, men so injured returning more often and more rapidly to duty than casualties of other types. A critical analysis of the data obtained yielded very useful information regarding the lethal quality of various weapons, vulnerable areas of tanks, figures for rate of crew replacements, and the nature and anatomical distribution of wounds. Such data provided knowledge of fundamental interest not only to designers of tanks and students of tank tactics, but also to those responsible for arranging the collection and care of the wounded.

The work of the Armoured Fighting Vehicles Sub-committee and the Lulworth research team proved so valuable that when the U.S.A. entered the war the American Army authorities sent representatives to report on the arrangements, and forthwith set up an organisation with generously equipped laboratories to undertake similar studies. A most happy and useful collaboration between the British and American establishments followed, and much of the pioneer work carried out at Lulworth was confirmed by the American investigators.

### THE DIRECTORATE OF BIOLOGICAL RESEARCH, WAR OFFICE

Early in the war there had been appointed a Scientific Adviser to the Army Council, to give advice on matters relating to weapons, equipment and allied problems. This post was filled by an eminent civilian physicist. There was also a General Staff Directorate of Research, charged with the study and analysis of the lessons of war and the production from them of tactical and organisational doctrine for the immediate and future role of the Army and for its co-operation with the other Services. Finally, there were the operational research groups of the Ministry of Supply, investigating in the field problems, physical in nature, relating to weapons and equipment.

In 1942 there was created within the Army Medical Directorate, the post of Director of Medical Research, whose immediate task was to act as liaison officer with the Medical Research Council and other civil and military bodies concerned with research affecting the interests of the Army Medical Service. This officer (Brigadier F. A. E. Crew), as representing the biological sciences, worked in close liaison with the Scientific Adviser to the Army Council, who represented the physical sciences. He was a member of the Military Personnel Research Committee and other M.R.C. committees. He also attended the staff meetings of the Ministry of Supply operational research groups and took part in such discussions as had biological aspects. Later, the title of the post was changed to that of Director of Biological Research. Two of his most important functions were to provide statistical machinery for the assistance of the Army Medical Department and to maintain a research pool capable of carrying the officers employed on whole-time investigations.

Among the research projects undertaken at this time were an analysis of preventable wastage during the course of a very large scale field exercise and a study of the moral effect of weapons. The former study, which concerned an exercise which was a rehearsal for the North African invasion, showed that there was a very considerable loss during the initial stages from blistered feet among labour units. The latter indicated that there is no obvious correlation between the tendency to fear a particular weapon and the likelihood of being wounded by it; that the attitude towards a particular weapon is derived from a mixture of logical and illogical processes; that the irrational dislike of a weapon does not tend to grow less following repeated exposure to its action, and that our troops certainly did not view enemy weapons in terms of muzzle velocities and fragmentation. As a result of this study it was recommended that investigations should be extended to include the reactions of enemy troops to our own weapons. Other subjects of investigation included an analysis of the quality of Army personnel; time and motion studies of gun-drills; a study of the secondary effects of bombardment; a study of methods for the collection and assessment of information coming back from the battle front; a study of accidents during training and caused by anti-personnel weapons; a study of symptomless foot defects in a fully trained infantry brigade; personality studies of German prisoners-of-war; a survey of medical problems of airborne troops; a survey of medical problems of combined operations; a survey of medical problems of ski troops; a study of the factors involved in night fighting; a study of medical problems involved in sonic warfare; and a study of rehabilitation problems among repatriates.

In December 1943, a complete branch of the Directorate of Biological Research was transferred to the Scientific Adviser to the Army Council, who now assumed responsibility for the provision of information dealing with physiological and psychological aspects of warfare other than medical, such as fatigue and battle stress, training, weapon design, and moral effects of weapons and tactics. The Directorate was reorganised, so that it could deal with the analysis of data of medical interest collected by the existing statistical mechanisms of the War Office. Its title was changed to that of Directorate of Medical (Statistical) Research, and a biological statistician (Professor L. T. Hogben), who later became Deputy Director, was accommodated on the Research pool. Its staff was henceforth recruited from amongst those with statistical knowledge and its chief tasks were to render statistical help to the directorates and branches of the Army Medical Department, to undertake original statistical investigation and to continue to maintain and administer the research pool. It provided information that was related to operational planning in so far as the medical services were concerned, to the construction of general administrative policies, and to the assessment of the value of new therapeutic measures.

The history of the Directorate shows that in a protracted war for which a nation is initially unprepared there are two distinct phases in the adaptation of scientific research to comply with military demands. In the early stages, the major problems are those arising from the necessity of producing in ever increasing quantity, machines and equipment of ever expanding ingenuity, precision and lethality. Later, the more pressing problems are those which relate to the numbers and quality of men, to their health, efficiency and morale. In the Second World War, the Fighting Services leaned heavily upon the physical sciences for the production of weapons and equipment. Later, they were forced by shortage of man-power to turn to the biological and social sciences for the satisfaction of their most urgent requirement—the provision of personnel capable of making the fullest possible use of the tools with which physical science had so abundantly endowed them.

## Work for the Royal Air Force

### THE FLYING PERSONNEL RESEARCH COMMITTEE AND ITS SUB-COMMITTEES

The history of aviation medical research in the Royal Air Force goes back to the period of the First World War. Already in 1917 the rate of flying accidents due to physical defects had been reduced by one fifth by this means and in 1918 knowledge of the effects of anoxia at altitude had led to the compulsory use of oxygen at 16,000 ft. Between the wars, work on visual problems of flying had included studies of the significance of ocular muscle balance for the visual judgment of pilots in landing aircraft (Livingstone, 1948). Research in association with the Department of Education of the Deaf, Manchester University, had revealed the occurrence in pilots of high tone deafness, which was regarded as a late result of exposure to aircraft noise; the efficient protection given by a close-fitting flying helmet against this hazard had also been demonstrated (Dickson, 1942). A standard method of assessing auditory acuity by audiometer had been suggested, both to avoid acceptance of deaf candidates for flying and to permit assessment of the effects of aircraft noise on serving aircrew (Dickson *et al.*, 1947; see also Chapter XVI, Oto-rhino-laryngology, in the Surgery Volume). From basic work during the First World War by Flack and others, tests for fitness for flying had been formulated. Blacking-out had become a problem in the Schneider Trophy pilots of 1929, and its cause and prevention were investigated in flight by medical officer pilots. Studies of glare in Iraq in the early thirties had demonstrated two factors of significance in night air fighting —the individual variations in capacity to appreciate very low light intensity and to synthesise form, respectively—which led ultimately to the development of the R.A.F. rotating hexagon test of night vision. Until 1936, the supply of candidates for flying had been greater than the

demand, and there had been no difficulty in maintaining the very high standard of efficiency laid down. R.A.F. expansion in the following year, however, completely changed the situation. The demand for pilots increased to such an extent that it was necessary to accept experimentally 100 sub-standard candidates and to find out from their subsequent performance how far standards could safely be lowered. Hitherto, failure in the physical efficiency tests had been regarded as an indication of inaptitude for flying or inability to stand the strain over a number of years, but the high wastage rate of 30 per cent. after preliminary training made it clear that these tests covered only a part of the field. Before the war broke out in 1939, means were being sought to reduce the existing costly experimental training. A mechanical method of testing for good arm-leg co-ordination (an essential attribute of the successful pilot) was being developed for use at the first examination to predict aircrew efficiency, apparatus for the purpose having been designed by a member of the staff of the Medical Research Council. High altitude problems were becoming urgent. The record ascent to 54,000 ft. in 1937 by a pilot wearing an early type of pressure suit had been medically supervised, and the dietetic requirements for long flights at altitude, in relation to the increased expansion of intestinal gas, were being examined.

The state of aviation medical research in other countries had as far as possible been assessed. American work was known by repute, and contact had been established in 1937 with American and Canadian workers visiting Europe. France was known to have paid attention to temperamental suitability for flying, Belgium and Japan to high altitude problems. When war broke out few data were available about Russian activities in this field, but it became known in 1941 that they had used the swing test for air sickness and had studied aircraft design on an anthropometric basis in the preceding years. The thoroughness of the German Air Force organisation for personnel research had been observed by the Consultant in Ophthalmology in 1937; his subsequent insistence on the need for the R.A.F. to overtake the German scientists influenced the Air Staff decision to establish a research flight at Hendon airfield in 1938. In the same year the Director of Medical Services of the Royal Air Force urged the necessity for co-ordinating the R.A.F. research studies on medical and physiological problems and consulted the Secretary of the Medical Research Council on the best means of doing so. The resulting proposal to set up a scientific committee of the Air Ministry under independent chairmanship, with a membership of civilian scientists of standing in subjects bearing on personnel research, was supported by the Secretary of State for Air; and so was formed the Flying Personnel Research Committee in January 1939. A list of the war-time members of the committee and its principal sub-committees is given in Appendix II. A visit by the committee's Chief Executive

Officer to the U.S.A. in May 1939 resulted in the re-organisation of R.A.F. medical research. The physiological side was linked with experimental development and construction of new aircraft types (as had been urged in 1934 by Air Defence of Great Britain Command), and the psychological side was associated with the universities. In July 1939, the physiology team moved into three lean-to sheds at the Royal Aircraft Establishment (R.A.E.), and started work with apparatus borrowed from Cambridge University. In January 1940, the R.A.F. Physiology Laboratory was formally opened in hutments with a decompression chamber at R.A.E.; it was placed under the direction of Dr. B. H. C. Matthews, Assistant Director of Physiological Research at Cambridge. Originally lent by the University for six months, Dr. Matthews was invited by the Air Council to serve for the war period. His reputation in connexion with high altitude research attracted into the team a number of young scientists interested in physiological research, who elected to serve in the R.A.F.

The siting of the Laboratory was particularly apt. Not only did some of the war-time staff belong to R.A.E., but the unit became the physiology laboratory for a score of that Establishment's departments. The assistance afforded by the wealth of scientific knowledge and technical and industrial skill of R.A.E. staff enabled the always comparatively small R.A.F. unit to accomplish its war-time research with distinction. An accepted principle was that in order fully to appreciate flight problems, the medical research worker had to undergo practical experience of these problems and carry out much of his work in flight. As operational problems became more complex, purely medical observation no longer sufficed, and the staff was supplemented by medical officer pilots capable of flying the most modern operational aircraft. Throughout the war many members of the team took part in operational flights in order to verify experimental work done in the laboratory. From 1943 onwards medical officers on the staff carried out research in aircraft of the Experimental Flight, R.A.E., which were allotted for medical research. While special subjects became identified with individuals, the whole staff participated in varying degrees in all the work undertaken. In May 1945, the physiology team moved into more permanent accommodation, which henceforth was known as the R.A.F. Institute of Aviation Medicine.

In October 1939, psychological research was assigned to the Psychological Laboratory, Cambridge University, under the direction of Professor (now Sir) Frederic Bartlett, with a team composed partly of R.A.F. medical research workers and partly of workers for the Medical Research Council. It was in relation primarily to the expanding needs of psychological research for the Fighting Services, that the Medical Research Council in 1944 reconstituted their team in Professor Bartlett's department into a special Unit for Research in Applied Psychology, with the late Dr. K. J. W. Craik as its Director. After Dr. Craik's death in

1945, Professor Bartlett himself became Honorary Director of the Unit. In 1939, the Department of Physiology at Edinburgh University undertook laboratory experiments on altitude problems for the Flying Personnel Research Committee. Under the direction of Professor I. de Burgh Daly, the animal investigations included study of the causation of bends, effects of low temperature and of pre-treatment with oxygen on decompressed animals, and effects of ultra-violet radiation on resistance to anoxia. The effects of alcohol and of various drugs on the altitude tolerance of pilots were also investigated.

## Activities promoted by the Flying Personnel Research Committee at Different Stages of the Air War

The two basic physiological stresses of flight are the decrease in atmospheric pressure with increase in altitude and the changes that occur with sudden alterations of velocity. Their effects can be reduced, if not eliminated, by suitable methods of protection, but in emergency they may again be encountered in a major degree. The chief problems deriving from these stresses were anoxia and blacking-out, and since air-striking advantage depends largely on an efficient oxygen supply, the first effort was directed towards improving the wasteful oxygen system then in use.

### OXYGEN SUPPLY IN AIRCRAFT

When war broke out, a direct-flow oxygen system was being used; in bombers, oxygen was supplied at high pressure from cylinders, interconnected, placed at intervals in the aircraft. Aircrew moving about or lifting ammunition were cut off from the supply and in danger of sudden collapse if they were out of reach of the plug-points along the length of fuselage. Some strapped a cylinder (14½ lb. charged) to their shoulders as a precaution. As range increased, more and more cylinders had to be loaded in the aircraft, taking up valuable space. The mask in use sometimes leaked, and crews complained of cold at altitude.

The R.A.F. Physiology Laboratory designed and developed the economiser-and-mask system, a constant-flow apparatus which effectively introduced into the lungs the correct amount of oxygen during inspiration and by storage wasted none during expiration—hence the name 'economiser'. The new apparatus was in practical use by July 1940, and thanks to the co-operation of the Instrument Division, R.A.E., 1,000 sets were produced in that year. An effort to separate oxygen from the air during flight, as a further economy, was abandoned when the resulting apparatus proved too heavy for use in aircraft. The principle, however, was later adopted for trans-Atlantic developments. The development of an anoxia meter (Goldie, 1942), for estimating the oxygen content of the blood, marked a great advance in evaluating various kinds of oxygen equipment.

INDOCTRINATION

It soon became apparent that, even with efficient breathing equipment, aircrew were often unaware of the dangers of the misuse of oxygen. Accordingly, in May 1940, courses of lectures for officers of the medical and flying branches were started in the decompression chamber at the Physiology Laboratory; among the subjects dealt with were the correct use of oxygen, the physiology of low pressure, the nature of bends, the physiology of night vision and the causation of air sickness. Films were used to demonstrate behaviour in flight under various stages of anoxia, and the students were given the opportunity of observing its effects on their fellows undergoing tests in the chamber; it became popular for pilots to bring their gunners to see the influence of anoxia on gunnery performance as demonstrated by the 'machine-gun test'—an apparatus invented by a member of the Medical Research Council staff. Widespread indoctrination became possible with the advent of mobile decompression chambers, which were designed and developed by the Physiology Laboratory in 1941. Since news of any failure of equipment quickly got round the squadrons, the reasons for incidents and counter measures adopted were carefully explained during the educational sessions, with good effect upon morale.

GERMAN INVASION OF HOLLAND (MAY 1940)

The successful use of paratroops by the enemy impelled the Army to arrange the large-scale training of paratroops in the summer of 1940. The Royal Air Force was responsible for training these men, who consisted of volunteers drawn from various regiments. From 1941 until the end of the war a Royal Air Force Medical Officer, himself a trained parachutist, who maintained close liaison with the Physiology Laboratory, was attached to the Central Landing Establishment, Ringway, to study methods of preventing injury during jumping, and the morale problems of training. The techniques of selection and training thus evolved in collaboration with the Instructors eventually reduced the wastage under training to 0·5 per cent. of jumps.

EARLY SORTIES (1940–41)

Many aircraft were still flying with the older oxygen equipment at this time. Cases of severe anoxia occurred chiefly among air gunners in their exposed positions; the cause was traced to icing in the mask inlet. This discovery stimulated work on the prevention of ill-effects from extreme cold from whatever cause. Progressively more efficient oxygen masks were evolved during the war until, late in 1945, the Type H mask was adopted by Great Britain, the United States and Canada; it incorporated a very small microphone for intercommunication, developed by the Royal Canadian Air Force.

Environmental conditions in aircraft were improved. With the help of the Chemistry Division, Royal Aircraft Establishment, work was undertaken on the prevention of contamination of cockpit air by carbon monoxide and other gases. Acceptance limits in this respect were imposed on the aircraft industry. A portable oxygen set for aircrew moving about large aircraft was developed in association with the Instrument Division, R.A.E. During this period, members of the Medical Research Council staff investigated methods of improving aircraft heating; they tested electrically-heated clothing and sweat-diminishing agents in the laboratory, and examined the relationship of the metabolic rate to endurance of cold.

### BATTLE OF BRITAIN (JULY—OCTOBER 1940)

During the period of daylight attacks, when every fighter in the air counted, a method was devised of cutting refuelling time on the ground to a minimum. A minor alteration was made to the oxygen system, by which it became possible to re-charge the cylinders without removing them from the aircraft.

Thanks to the work of Cotton, Franks and others (e.g. Stewart, 1945), British pilots had the advantage over their opponents of greater manœuvrability during 'dog-fights'. It was already known that unconsciousness occurred for a few seconds after blacking-out without the knowledge of the pilot, that abdominal belts, although seeming to delay the onset of symptoms, eventually produced unconsciousness, and that a crouch posture raised the blacking-out threshold by 2 *g*. Accordingly, at the expense of only a small alteration to the aircraft structure, a position a few inches above the normal foot position was added to the rudder pedal, so that the pilot could instantly assume a crouch during combat.

A valuable aid to escape from altitudes above 30,000 ft. was provided by a ten-minute supply of oxygen, stowed in the dinghy-parachute pack; this sufficed to enable the pilot to bale out in safety and to preserve consciousness during the fall to levels at which oxygen is no longer required. To determine the correct flow of oxygen necessary to maintain the personnel at as near ground level conditions as possible at every variation of altitude and rate of work performed, an extensive flying programme was undertaken by the physiology team; they carried out many tests of efficiency in circumstances corresponding to different operational situations.

With the increase of night bombing attacks and R.A.F. night interceptions towards the end of this phase of the war, much work on the practical and physiological problems of night vision was undertaken (Livingston, 1942, 1943, 1944, 1945). It was recognised that only rarely in the British population was a night visual defect of significance likely to be encountered, but the hazard thus involved justified prolonged

investigations. Some 220,000 tests of night visual acuity were undertaken by means of the R.A.F. hexagon appliance, which examined six subjects at a time and exhibited for identification a series of letters and objects under accurate illumination corresponding to definite night conditions. In addition, rod scotometry was carried out by means of luminous beams of known brightness, by which it was possible to plot a field of night vision using a red source of light for fixation (Livingston, 1944). It was found that between 3 and 4 per cent. of the population of aircrew age had defects in visual perception in low illuminations which handicapped their efficiency.

Analysis of the sites of missile wounds and burns during the period of heaviest air attack, May-June 1940, revealed that the pilot's body was relatively well protected by the aircraft, and that the majority of wounds affected the limbs. It was found, moreover, that about 80 per cent. of burns were received on the face and hands unless these were protected by the mask assembly and by flying gloves; to reduce this serious risk to aircrew, the wearing of protective equipment (helmet, goggles and flying gloves) was made compulsory.

Directly related to the safety and efficiency of aircrew was the clarity with which the whole process of raid reporting was visually presented in Sector Operations Rooms of Fighter Command to all those who had to make decisions on the deployment of fighter forces. An analysis of the work situation was made in the Psychological Laboratory, Cambridge, as a result of which apparently minor changes in the features of the Control Room equipment were suggested—a slight increase in the size of some critical detail and slight alterations to increase the contrast between background and display—which enabled everyone concerned to have a clear view of the plotting table display, without having recourse to binoculars in an attempt to compensate for the difficulties of the viewing conditions (Bartlett and Mackworth, 1950).

### BATTLE OF THE ATLANTIC (JULY 1940–MAY 1943)

The introduction of Catapult Armed Merchantmen brought with it the problem of protecting the pilots operating the Hurricanes from these vessels against the hazards of immersion on baling out in northern and Arctic waters. Experiments with suits made of various materials, carried out by a member of the Physiology Laboratory in Icelandic waters and off the Orkneys during winter, led to the development of a suit resistant to rain and sea-water; the suit also had the advantage of being comfortable at standby on the ship, as the material of which it was made allowed perspiration to take place through it (Pask, 1946).

As the war progressed, all possible means were explored to avoid wastage in personnel and to prevent fatigue from various causes encountered in flying (Reid, 1948, 1949; Symonds, 1943). The Psychological Laboratory, Cambridge, undertook studies with the object of

distinguishing the fighter from the bomber type of pilot by psychological tests at the Initial Training Wing, Cambridge. In the event, the tests did not prove sufficiently reliable for Service use, but they served as a guide to later studies of temperamental suitability for operational flying.

Scrutiny of existing flying accident reports revealed a lack of information on the human element. Accordingly, a medical officer was detailed to investigate human failure as a cause of accidents. A better method of reporting accidents was devised as a result of surveying the nature and sites of injuries sustained during crashes over a significant period. Under this system data were provided for statistical analysis and it was possible to use suggestions made by medical officers for reducing the number of accidents. Other work included a study of the rates of landing accidents at the end of operational sorties of different lengths, and an investigation of the hazards of escape in air combat.

A Vision Committee was formed in 1941 to examine such Service visual problems as the presentation of aircraft instruments, daylight scanning, and the visual problems of night flying—including dark adaptation, take-off and landings in the black-out, the training by day in aircraft recognition at night by use of goggles simulating moonlight brightness, and the selection of personnel for important night operations who were specially gifted visually. Among other subjects studied were the reduction of visual range with the interposition of 'Perspex', and the effects on vision of diet and anoxia.

The luminosity of the night sky was measured in flights under all conditions of moonlight, starlight and cloud formation, and possible ranges of vision were plotted against the size of objects. Jointly with R.A.E., a physiological investigation of the best methods of illuminating cockpit instruments and maps was undertaken. The interference with vision of the structure of turrets and cockpits was analysed, leading to improvements in design, especially in turrets. Various methods of night vision training were tested and the resulting improvement in night vision assessed. Experiments with contact lenses as a protection to the eyes while making observations through clear vision panels in aircraft (small unglazed apertures) showed that, in general, these lenses were valuable to pilots who had good tolerance and who required visual correction; in particular cases men were able to fly on operations who would never have been acceptable when wearing corrected goggles. Pilots with normal eyesight, however, derived no benefit, as they were impatient of the manipulations necessary in adjusting the lenses.

Extensive field trials on the military uses of dazzle were organised by a special panel in association with other Service Departments (Stiles, 1947). Responsibility for assessing the intrinsic merit of all visual aids proposed for Service use was undertaken by another panel, which also had the unenviable task of dealing with faults in goggles already in use.

The latest types of fighter aircraft called for more effective protection than the postural method against the ill-effects of sudden changes of velocity (high *g*). In 1941 the first of the anti-*g* suits, a water-filled garment developed by the Royal Canadian Air Force, was flight tested in collaboration with its inventor and was commercially produced for trials in sub-tropical and tropical theatres. Despite its value in reducing fatigue, it was never adopted for the R.A.F., because of its general discomforts, especially in hot climates. Extensive tests were undertaken in 1943–4 of the R.A.F. air-activated suit, then under development in step with similar developments in America. The new R.A.F. suit proved the most efficient, comfortable and easy to put on of any yet produced, and it was used in operations in the closing phase of the war in Germany.

The interest in the effects of acceleration was extended to the study of air sickness in bombers, coastal reconnaissance aircraft and in gliders (Winfield, 1942). Investigations indicated that the cause was largely the repetition of vertical acceleration on gusts. A Sub-committee on Air Sickness, operating between 1940 and 1942, maintained contact with other Service and civilian committees studying this problem, and reviewed all the known or reputed remedies. Members of the Medical Research Council staff contributed to knowledge of the subject; one, as the result of a study of the pathology of air sickness, advanced the opinion that the utricle was the organ concerned; others demonstrated from laboratory experiment that adaptation by swing tests was effective for a period only. Motion sickness due to disturbance was distinguished from the sickness which arises from an anxiety state (Symonds *et al.*, 1947). Apart from the elimination of aggravating factors such as vibration, noise, smells, diet and fatigue, hyoscine was found useful as a prophylactic.

The influences of various drugs, both stimulant and narcotic, upon altitude tolerance were investigated, as well as the effect of the current treatment for malaria. The value of amphetamine as a means of keeping crews alert was the subject of extensive research by the R.A.F. team (Browne, 1946, 1947) and by members of the Medical Research Council staff (Davis, 1947). Although the drug was shown to have certain disadvantages, its use was recommended, under medical supervision, in situations of stress where sleep was a threat to performance.

### LEND LEASE (MARCH 1941)

Special investigations relating to high altitude bomber operations were carried out with the early Fortresses sent by the United States to Great Britain under Lend Lease. Their oxygen installations were found to be inadequate for the air war, and special equipment for all these aircraft was constructed in the R.A.F. Physiology Laboratory. The great difficulties of bomber operations at 30,000 ft. became apparent

during these studies, and the experience was invaluable in improving oxygen equipment and operational procedure in its use for very high altitude work. In addition, all the Fortress crews were tested for susceptibility to bends, and important information was obtained about the frequency of the occurrence of bends in flying personnel.

American aircraft ferried to Britain during the winter of 1940–1 were obliged to fly very high for protection against the weather and against enemy attack, with the result that the passengers, who were for the most part individuals engaged on important missions, often suffered from frostbite—one extreme case requiring amputation of both hands. The cause was traced to failure of the heating installation together with an inadequate supply of oxygen. Further investigation showed that the ideal of toughness amounted to a fetish among Canadian aircrew, many of whom had been pioneers on the Arctic air routes and were not accustomed to the requirements of military aircraft. Neither pilots, crew nor ground staff had at that time realised the necessity for an efficient oxygen supply. An intensive educational programme on the R.A.F. pattern was therefore immediately organised at all flying training schools in Canada.

The next aim was to achieve standardisation, or at least interchangeability, of essential parts of equipment between American, British and Canadian aircraft. The key to the problem was the size of the microphone in the headgear assembly, and as soon as the small R.C.A.F. microphone was jointly accepted, the oxygen-intercommunication equipment was rapidly standardised.

### BATTLE OF MALTA (JANUARY 1941—OCTOBER 1942)

At this period of intensive night air activity on the Island, the night vision of the aircrews was of particular importance. A nutritional and ophthalmic specialist team visited Malta in 1942 and examined the dark adaptation threshold of a large group of men, using a slit-lamp and adaptometer technique. They found that only two persons possessed normal dark adaptation thresholds, although aircrew had been receiving a special issue of vitamins A and C. Most of the men were unaware that their night vision had deteriorated, since the whole population was in the same state; a few admitted to having difficulty in night landings. Here, as in earlier studies in West Africa and in the Sudan, the deterioration seemed to be directly related to a deficiency of fresh vegetables and fruit in the diet. A dramatic improvement of night vision was observed in some of the pilots on leave in Egypt from Malta, after only a week during which they had access to plenty of fruit and vegetables. At this time a more favourable turn of the war permitted a general improvement in diet, and the nature of the factor responsible for the effect on night vision remains undecided.

### WESTERN DESERT CAMPAIGN (1940–3)

Similar nutritional investigations in this theatre indicated that the British units, supplied with the British field ration, were worse fed than the American troops. The Australian troops, who were officially on the same ration as the British, had managed to supplement it with hundreds of tons of tinned fruit captured at Tobruk, which was portioned out in four large issues per week. Examination showed that the dark adaptation thresholds of the American and Australian personnel approached normality (6·6 millilamberts) but the British showed abnormally high thresholds, the degrees varying with the time spent in the Western Desert. The British also showed abnormally dry skin conditions likewise attributed to dietary deficiency (Macrae *et al.*, 1943, 1944).

### THE BOMBER OFFENSIVE (1940–5)

The need for large numbers of pilots to operate the mounting bomber offensive led to an investigation of all possible sources of wastage. Analyses of the data of Bomber Command sorties showed that the highest landing accident rates occurred after short sorties of less than two hours and after long sorties of ten hours or more. These results, together with those obtained from a study of the errors made by navigators and pilots during operational sorties, confirmed results derived from laboratory studies of pilot error (Davis 1946, 1948), in which 'fatigue' was excluded as an important cause of error. The cause was now thought to be a psychological tension which varied with the demands made upon the pilot by the situation. In the laboratory experiments, two sorts of error were observed: those of over-action and those of inattention.

Particular attention was paid to the stresses of high altitude flying. The symptoms, causes and prevention of bends had been studied since they were first observed in experimental decompression simulating altitudes greater than 30,000 ft., when pains in the joints and limbs, paralysis or sudden collapse and certain forms of blindness had been experienced by the research subjects although no anoxia was present. The same symptoms had been observed in a highly selected sample of Service population—members of the High Altitude Photographic Reconnaissance Flight. Decompression chamber experiments in 1941 demonstrated that bends did not occur immediately on reaching 30,000 ft., but developed in predisposed subjects between 30,000 and 37,000 ft.; it was also found that frequent spells of duty at high altitude produced apathy and distress not attributable to anoxia. As a result, aircrews for operational duties involving long flights above 30,000 ft. were subjected to standard tests designed to exclude susceptible individuals. Facilities for breathing oxygen before flight were provided at squadrons for aircrew who wished to use this method of delaying the onset of bends—research had proved that it did not prevent their occurrence.

The precise cause of bends remains unknown, but an obvious solution was the provision of pressure suits and pressure-cabined aircraft.

The development and flight trials of pressurised aircraft in 1941–2 were followed by a preliminary assessment of the physiological effects of explosive decompression (that which occurs in less than one second); it was concluded that while such rapid decompression contained an element of risk under certain conditions, it was unlikely to have ill-effects on healthy individuals flying at 44,000 ft. or below, with a differential pressure not greater than 5 lb./sq. in., provided that adequate precautions were taken simultaneously against anoxia and bends.

In June 1941, the Germans had a temporary altitude advantage of about 1,000 ft., due to their method of fuel supply. As an interim measure until more pressure-cabined aircraft became available, the pressurised waistcoat was brought rapidly to the final stage of development in association with the Royal Canadian Air Force. The basis of this garment was the R.A.F. flotation stole (the 'Mae West'), which had been adapted at Wright-Patterson Air Force Base Laboratories to deliver oxygen at a specified pressure. The waistcoat, pressurised at one-third of a pound, gave a ceiling of 41,000 ft., at a real altitude of 45,000 ft.; it could serve also as an emergency flotation stole.

During 1942 the operational altitude of heavy bombers had generally increased; new types of gun turret with open panels meant the routine exposure of aircrew during night flying in winter to temperatures of −40° C. and below. Under such conditions, serious inefficiency in air gunners could be prevented only by the provision of electrically heated clothing comprising inner linings, gloves and boots, with the heat distributed in physiologically correct proportions to the hands, feet, and trunk. By 1944 this equipment was fully developed with the co-operation of industry and the electrical experts of R.A.E. In view of the physiological and practical limits to the degree of protection afforded by the type of clothing composed of a wind-resistant outer cover and an insulated inner lining, when no heated clothing is used, the 1945 patterns were made up in special new fabrics devised for the purpose by the British Cotton Industries Research Association. Gloves, boots, draught protectors for exposed parts of the face, were also developed; flying helmets were improved to combine the greatest comfort under varying climatic conditions with adequate exclusion of sound. Correct sizing of garments was based on anthropometrical surveys of many thousands of aircrew (Morant, 1947, 1948, 1949).

The formation of the Path Finder Force in August 1942 produced a problem in which air bombers had to estimate by eye the average position of a number of target indicators. The target was usually in some heavily defended area with severe operational hazard. Controlled human experiments at the Psychological Laboratory, Cambridge, revealed the main causes of the difficulties experienced and determined

which features of the situation could be incorporated in synthetic training. As a result, a bomb-aiming apparatus was designed and developed which was adopted by Bomber Command for synthetic training purposes (Bartlett and Mackworth, 1950).

Recognition of the progressive nature of aviation deafness led to the analysis of aircraft noise and to work on the development of protective measures, in which many Departments collaborated. The Otological Committee was formed in 1943 to examine relevant problems. An outstanding advance was the introduction of a new hearing test of ability to interpret speech against a background of synthetic aero-engine noise, for which the R.A.F. Acoustics Laboratory developed the necessary apparatus; this laboratory was also responsible for calibration of the audiometers used in the test (Dickson *et al.*, 1947; see also Surgery Volume, Chapter 16).

Complaints of the occurrence of dental pain at high altitudes were investigated by the dental research teams (Harvey, 1943, 1944) and were found to be related to the materials and procedures used for fillings. It was also found that the pain was caused not by temperature but by the effects of low pressure. Conservative dentistry in the R.A.F. was accordingly altered. In 1945 mass dental radiography was suggested to detect early interstitial caries not apparent on inspection. A bite-wing X-ray method was developed for this purpose, which included use of a film holder, designed so that the patient kept the film in place in his mouth by biting on a metal plate $\frac{1}{8}$ in. thick, at right angles to the film; this plate also protected the centre of the film on which was embossed the identification number which had been stamped on by hand percussion press (Harvey, 1946). The method was used successfully during a survey of the effect of fluorine on dental caries which was started in April 1945.

In 1942 the Physiology Laboratory began to investigate the dangers of unconsciousness, even of death, from anoxia, when baling-out from the stratosphere. This work led to further researches on baling-out or ditching in the sea, and to the development of protective suits to minimise the risks involved. By 1945 a special inflatable exposure suit had been designed for aircrew to put on either just before baling-out or ditching, or after entering the dinghy. This suit was carried in the stole of the 'Mae West'.

In 1943 the effectiveness of various life-saving jackets was assessed on a subject, continuously anaesthetised and immersed (Macintosh, 1945). These hazardous experiments were of great value in determining the correct disposal and the total amount of flotation necessary to keep the nose and mouth of an unconscious individual clear of the water. The anaesthetised subject was also used to determine the best method of performing artificial respiration.

In collaboration with the Admiralty, Air Sea Rescue Services and with other laboratories and industry, methods of preserving life were

developed which included extraction of drinking water from sea water by chemical desalination or by the use of various kinds of still; work to determine the best type of survival ration was also undertaken, and a drill was evolved for adoption in a dinghy over a period of days.

In 1943, in collaboration with the Mechanical Engineering Division, R.A.E., a programme of research and development was carried out on aspects of the structural strength of the human body, with a view to reducing the mortality or injury rate in the deceleration of crash landings or ditching; safety harness, safety cells and aft-facing seats were physiologically tested, and data were collected from unsuccessful suicide attempts. This work showed that the human body, if adequately supported, was stronger than the overall structural strength of the aircraft for decelerations of short duration.

Investigations of psychological disorders in R.A.F. flying personnel were begun in 1942, with the aim of enabling the medical branch to give authoritative advice to the executive on the operational limits of aircrew (Symonds, 1943; Symonds *et al.*, 1947). It was found that about two-thirds of the individuals who failed to withstand the stress of flying were predisposed to nervous breakdown. As this group undoubtedly included individuals capable of adapting themselves, it was decided that only the severely predisposed should be rejected at entry. The attention of medical officers and of flying instructors was accordingly directed to signs of temperamental unsuitability for aircrew duties. Data from these investigations were statistically analysed in regard to types of flying duty associated with breakdown, types of nervous breakdown, the quantity and quality of aircrew service rendered by men with psychological disorders who were accorded a full category by neuro-psychiatric specialists and returned to duty after recovery, and the reliability of the psychiatric method of diagnosing psychological disorders in flying personnel. (See Medicine and Pathology Volume, Chapter 15.)

In response to a request by the flying training side for assistance in predicting, either from selection tests or from performance in training, what aircrew were likely to fail in operational flying on account of temperamental unsuitability, a field experiment was undertaken in 1943 on over a thousand pilots who had completed flying training and were awaiting operational training as heavy bomber pilots. The results of assessment by psychiatric interview or psychological tests at the initial examination were to be compared with the operational performance. The end of the war prevented about two-thirds of the subjects tested from proceeding to Bomber Command, so that only a few completed the tour or experienced the strain of operations. This considerably upset the validation of the experiment, the conclusions from which could be regarded only as indications of methods of approach which might be fruitful in post-war studies. It was clear, however, that psychiatric assessments, particularly those by specially experienced

psychiatrists, were related to psychological failures in training and had value in assessing leadership and morale. Two of the psychological tests used had special merit, although the form of neither was suitable for inclusion in the test battery: the Cambridge Cockpit Test was promising for detecting individual liability to accident (Davis, 1946, 1948), and the after-contraction of muscle test was useful for determining liability to repeated accidents.

Throughout the war the adaptability of the human body, aided by the studies of the physiologist and the psychologist, enabled aircrew to master many of the stresses of flight (Matthews, 1944, 1945, 1946). But there were serious limitations to the extent to which the body could adapt itself to some of these stresses, and it became apparent that aircraft construction would need modification with a view to eliminating the basic causes. Attempts to solve individual problems proved impracticable—the physiological adjustment of one component threw others out of balance. The first serious attempt to solve the workspace problem was made in 1945, as a result of earlier studies of injuries due to crash hazards of aircraft structure, and of accidents due to misuse of controls. The advent of the ejection seat required that clearances for all sizes of pilot should be adequate. The particular features of the aircraft workspace naturally varied with the role of the aircraft. The critical maximum and minimum pilot dimensions likely to affect cockpit design had, however, already been determined by anthropometry. A combination of expert knowledge in physiology, applied psychology, anthropometry, aircraft design, and a wide range of flying experience was co-ordinated in the Cockpit Layout Committee of the Ministry of Supply, formed in February 1945, to examine the problems of cockpit layout in military aircraft and recommend a policy to be adopted. Starting with a skeleton single-seater cockpit, constructed on basic requirements, a mock-up cockpit was built in which the position and mode of operation of some 200 instruments and controls were experimentally worked out, the whole being submitted to test by pilots of long and varied experience.

### THE BURMA CAMPAIGN (DECEMBER 1942—JANUARY 1945)

To pilots operating over the jungle, the greatest cause of anxiety was the fear of falling into enemy hands. Special survival equipment was therefore developed for aircrew to replace the blue uniform, which was too heavy for comfort and too conspicuous for evasion. Special foot-wear and lightweight flying overalls were designed, with suitable rations and the various articles of survival kit disposed in the many pockets.

After preliminary observations of tropical conditions in the South-West Pacific theatre, further investigations were carried out in the forward areas of India and Burma. Heat effects on aircrew and on

ground crews servicing aircraft in the open were studied, and remedial measures in regard to acclimatisation problems were suggested.

At the end of the war it was established that the Mark II oxygen economiser provided the simplest and safest method of supplying oxygen in use by any of the combatant air forces; while from post-war interrogation of German aviation physiologists it became obvious that Allied aviation medical research had caught up with the German effort about 1943.

During the war period, every effort was made to avoid overlapping of aviation research by close liaison with comparable activities in the other Commonwealth countries and in the U.S.A. Laboratory workers exchanged visits, and detailed reports of researches were exchanged with the National Research Council of Canada, the Royal Australian Air Force Flying Personnel Research Committee, the Air Personnel Research Committee of South Africa, the Committee on Aviation Medicine of the Division of Medical Sciences of the National Research Council of the U.S.A., and the Committee on Medical Research of the Office of Scientific Research and Development of the U.S.A., to the advantage of all.

## Publications relating to Chapter 2

Only a relatively small proportion of the work promoted by the Personnel Research Committees has been published; much of it was presented in the form of unpublished reports to the Service departments; these, not being generally available for consultation, are omitted from the lists below. In addition to papers recording the results of particular researches, the references include some general articles reviewing, in somewhat greater detail, a number of the researches briefly mentioned in this chapter. A few of the publications listed deal with relevant studies not specifically mentioned in the text.

Although the publications have been grouped according to the Service for which the work was primarily undertaken, it should be borne in mind that many of the studies mentioned under the heading of only one of the Services were in fact of interest to all three, as well as having general medical interest or a bearing on peace-time problems of industrial health and productivity.

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# CHAPTER 3

# WOUNDS AND INJURIES

In this chapter are reviewed some of the principal studies by British investigators between 1939 and 1946 which had a direct bearing upon the treatment of wounds, burns and other injuries and their systemic effects. Since the chief use of blood transfusion in time of war is to resuscitate the injured, the history of British research on blood transfusion, blood grouping and blood products during the war is also included in this chapter, although many of the studies described have important practical applications outside the field of traumatic surgery. The account given here of work on the prevention and treatment of wound infections naturally includes references to the use of penicillin for the purpose in the later stages of the war, but the history of the development of penicillin as a medicinal agent, including the laboratory and early clinical studies of its application to wound treatment, is recorded in greater detail in Chapter 7.

Problems of wound ballistics are described in Chapter 11, as are the special features of air and underwater blast injuries. A brief review of the wartime studies of 'crush injuries' (ischaemic muscle necrosis) is included in this chapter as part of the section dealing with traumatic shock.

## The Work of the War Wounds Committee and Its Sub-committees; with Some Related Investigations made Independently

### ORIGIN AND CONSTITUTION OF THE COMMITTEE

A War Wounds Committee, including representatives of the three Fighting Services, the Ministry of Health, the Department of Health for Scotland, the Ministry of Home Security and the Ministry of Pensions was appointed by the Medical Research Council in June 1940 with the late Sir Cuthbert Wallace as its first Chairman; its membership is given in Appendix I. The committee's terms of reference were to advise on the application of the results of research to practice in the treatment of war wounds and on the need for new investigations. The necessity for creating such a committee had become apparent during the campaign in France and Flanders, when owing to the speed of the enemy's advance westward large numbers of wounded had to be transferred to the United Kingdom before they could receive adequate surgical attention. By the time the patients arriving in these convoys

came under the care of a surgeon, infection of their wounds was often already of many hours' standing. A small proportion developed true gas gangrene of muscle and a much larger number had foul gangrenous wounds of the superficial tissues, in which bubbles of gas might be present and from which gas-forming bacteria could often be isolated. The clinical differentiation of cases of the second type from true gas gangrene is notoriously difficult; and it seemed probable at that time that many patients with superficial anaerobic wound infections, causing little or no toxaemia or risk to life, were, in fact, in danger of being too drastically treated, on the assumption that the condition of their wounds represented the initial stages of gas gangrene of muscle. Moreover, as regards both gas gangrene itself and these lesser forms of anaerobic wound infection, there was an urgent need for a co-ordinated scheme of combined clinical and bacteriological research to demonstrate the respective places of surgery, antitoxin and drugs in prophylaxis and treatment. Research upon the bacterial flora of wounds at different times after their infliction, and upon the use of the sulphonamides to prevent and treat streptococcal and other wound infections, also required direction and co-ordination. Local application of sulphonamides to wounds had already been started in the field in the French and British Armies, but much more work was needed to establish its value. There were many other practical problems demanding attention, such as the treatment of burns, and the merits and limitations of the 'closed plaster' treatment of limb wounds, which at this period was being extensively used as the result of the favourable reports received from surgeons who had applied it during the Spanish Civil War.

As the need arose the War Wounds Committee set up a series of expert sub-committees to study particular aspects of the pathology and treatment of wounds and injuries. These bodies, like the main committee, were composed both of Service representatives and civilians. The work they promoted or co-ordinated makes up the greater part of the content of the next ten sections, though certain important investigations carried out independently—for example, the work of Ungley and others on the nature and treatment of 'immersion limb'—are also described.

### ANAEROBIC WOUND INFECTIONS

One of the first acts of the War Wounds Committee was to prepare a memorandum on the diagnosis and treatment of gas gangrene, to which was appended a suggested scheme for the bacteriological investigation of war wounds, contributed by the Committee of London Sector Pathologists (Medical Research Council, 1940). In 1942 a special Anaerobes Sub-committee of the War Wounds Committee was appointed, and this body, as well as initiating an active research programme, shared with the main committee the responsibility of preparing a

revised edition of the memorandum (Medical Research Council, 1943).

Before the War Wounds Committee was established, the War Office had issued a special form—Army Form I 1241—for reporting cases of gas gangrene. This was amplified on the committee's recommendation so as to include a special supplement covering cases of the milder forms of infection by gas-producing micro-organisms, as well as of true gas gangrene. Despite the inevitable limitations of any investigation depending on records completed by many different medical officers, under the varied and difficult conditions of active service, statistical analysis of the information given on returned copies of Army Form I 1241 led to the conclusion that surgical treatment combined with the early administration of polyvalent gas gangrene antitoxin in adequate dosage gave significantly better results in gas gangrene of the extremities than did surgical treatment without antitoxin (Macfarlane, 1943, 1945.)

The value of drug treatment as an adjunct to surgery and antitoxin could not be assessed from the information on the forms, owing to the lack of uniformity in the nature and amount of the drugs used, and to the absence of controls. Evidence that sulphonamide drugs could act synergically with antitoxin in the treatment of experimental gas gangrene in animals had, however, been obtained, before the Anaerobes Sub-committee was appointed, by Henderson and Gorer (1940); and the War Wounds Committee had taken this into account in recommending, in the first edition of the memorandum mentioned above, that a combination of surgery, antitoxin and sulphonamide should be used in the prevention and treatment of the disease in man. This recommendation was repeated in the second edition of the memorandum (1943), with minor modifications, particularly as regards the dosage of antitoxin and the nature of the sulphonamide preparation to be used, which had resulted largely from the programme of clinical and experimental research co-ordinated by the Anaerobes Sub-committee in the meantime.

Apart from those concerned with the work on gas gangrene toxoids, discussed separately below, the centres chiefly contributing to the experimental research programme sponsored by the sub-committee were the National Institute for Medical Research, the Central E.M.S. Laboratory, Watford, University College Hospital Medical School, London, and the Middlesex Hospital. At the National Institute, systematic immunological studies of experimental *Cl. welchii* infection in guinea-pigs led to the conclusion that the α-toxin is the most important agent in the toxaemia and the α-antitoxin the essential factor in the antiserum (Evans, 1943 *bis*, 1945). It was thus fortunate that this factor was measured in the British standard preparation of *Cl. welchii* antitoxin, which along with those for *Cl. oedematiens* and *Cl. septicum*, had been renewed at the outbreak of war and aligned, as

usual, with the corresponding international standards. The value in *Cl. welchii*, *Cl. oedematiens* and *Cl. septicum* infections of the specific antitoxin if given sufficiently early was confirmed in subsequent experiments (Evans, 1945), as was the beneficial effect of the surgical relief of tension in gas gangrene. Work was also done at the National Institute on the prophylactic value against anaerobic wound infections of different sulphonamide drugs applied locally (Hawking, 1941; see also Chapter 7). A new sulphone compound, *para*-methylsulphonylbenzamidine or V187, prepared at the Institute, was found to be active against both gas gangrene and tetanus infections in animals (Evans, Fuller and Walker, 1944, 1945), but the end of the war came before it had received adequate field trial in man. Experimental work on the uses and limitations of antitoxin treatment for gas gangrene, with special reference to the causes of failure of late antitoxin treatment, was carried out at the Central E.M.S. Laboratory, Watford, and at University College Hospital Medical School (Miles and Miles, 1943); at these two centres, and at others, much attention was given also to the problem of the rapid bacteriological diagnosis of gas gangrene (Gordon and McLeod, 1940; Hayward, 1941, 1943; Hayward and Gray, 1946). At the Middlesex Hospital a number of different drugs and drug mixtures was tested against experimental anaerobic wound infections (McIntosh and Selbie, 1941, 1942, 1943 *bis*, 1946). The substances examined included penicillin, when it became available, and, earlier, a mixture of proflavine and sulphathiazole powders, which was used with some success in the Army and elsewhere for the treatment of infected wounds.

Among several interesting investigations bearing on the treatment of gas gangrene which were carried out independently of the Anaerobes Sub-committee, the work by Blomfield at Oxford University on the intramuscular vascular pattern of limb muscles is noteworthy (Blomfield, 1945; Le Gros Clark and Blomfield, 1945; Le Gros Clark, 1946). It is discussed more fully in the section dealing with injuries to blood vessels (below). The relationship of Blomfield's findings to the clinical incidence of gas gangrene in different muscles and muscle groups was demonstrated by Wood Power (1945).

In preparation for the invasion of Normandy in 1944, the War Wounds Committee, the Anaerobes Sub-committee and the Penicillin Clinical Trials Committee of the Medical Research Council co-operated with the Medical Departments of the Fighting Services and with the civilian emergency medical services in arranging a large-scale investigation of the value of penicillin and other drugs in the prevention and treatment of wound infection in casualties transported to Great Britain. Further reference to these studies and their practical outcome is made in the next section. Various pathological and biochemical studies of gas gangrene by expert teams in university departments were arranged at the same time and were carried out during

the subsequent campaign in North-west Europe. Owing to the small number of cases of gas gangrene encountered and the variety of treatments given, the results of the biochemical studies—undertaken mainly at the British Postgraduate Medical School, London, and at Birmingham University—were inconclusive; so far as they went, however, they supported the opinion reached by Wright, Colebrook and Fleming in the War of 1914–18 that gas gangrene is associated with an acidaemia; whether the biochemical changes in wounded patients with this disease differed significantly from those in patients with muscle injuries of comparable extent but without superadded anaerobic infection, could not be decided. Concurrently with these observations, combined field and laboratory inquiries into the possible role of products of tissue breakdown in the general toxaemia of gas gangrene were being made in the Army and at Oxford University (MacLennan and Macfarlane, 1945; Macfarlane and MacLennan, 1945; Robb-Smith, 1945).

One of the main objectives of the Anaerobes Sub-committee on its appointment was to develop toxoids for the active immunisation of troops against the more important clostridia of gas gangrene. Research on this subject was carried out at the School of Biochemistry, Cambridge, the Lister Institute of Preventive Medicine, London, and the Wellcome Physiological Research Laboratories, Beckenham. A powerful stimulus to undertake it was provided by the remarkable success achieved in the Allied Armies by the use of toxoid immunisation against tetanus (Boyd, 1946; Boyd and MacLennan, 1942). Considerable progress was made in the preparation and purification of gas gangrene toxoids suitable for clinical use, and trials in laboratory animals showed that active immunisation with the corresponding toxoid gave a high degree of protection against infection with *Cl. welchii* and *Cl. oedematiens*, though less against *Cl. septicum* infection (Robertson and Keppie, 1943; Rogers and Knight, 1946; van Heyningen, 1948). It was hoped that it might be possible to produce a combined toxoid which would protect troops both against tetanus and against the commoner gas gangrene clostridia. Owing to technical difficulties in the large-scale production of an active toxid of *Cl. welchii*, that hope had not been realised by the end of the war, though encouraging results had been obtained in small-scale trials carried out by the staff of the Wellcome Laboratories in groups of soldiers and civilian volunteers. Information of much scientific interest relating to the biochemistry of gas gangrene toxins and the immunising effects of clostridial toxoids was obtained during these studies.

Further work on immunological agents against tetanus and gas gangrene is described in Chapter 6, with particular reference to the supply and storage of large quantities of the antitoxins for emergency needs. Mention is appropriately made here, however, of a study carried

out at the National Institute for Medical Research early in the war, on the persistence of the immunity following injections of tetanus toxoid in man; it was shown that the antitoxin production obtained by giving a single 'boosting' dose of toxoid a year after the initial two injections was very large and enduring, and that frequently repeated boosting doses, as currently recommended, were unnecessary (Evans, 1941, 1943); it was also shown experimentally that the immune response to the antigenic stimulus of the boosting dose was not significantly affected by exposure to cold, moderate restriction of diet, or intercurrent infection (Hartley, Evans and Hartley, 1943). These findings had important practical and economic implications.

### THE PREVENTION AND TREATMENT OF WOUND INFECTIONS IN GENERAL

In the preceding section a brief account has been given of researches into the prevention and treatment of gas gangrene undertaken by British investigators during the war. Gas gangrene, however, is fortunately one of the rarest forms of wound infection; it is important only because of its severity and the danger it entails to life or limb; it is, moreover, particularly difficult to treat successfully with drugs, since it usually develops in lacerated muscle deprived of its normal blood supply—which means that medicaments injected or absorbed into the blood stream may not be able to reach the affected tissues. The study of the prevention and treatment of other types of wound infection was not only much wider in its scope, but was attended by a very much higher degree of clinical success.

A lesson learnt in previous wars, which nothing in the experience of 1939–45 has contradicted, is that the best way of preventing infection by the bacteria introduced into wounds at the time of injury is by early and adequate surgical operation; this should generally include the opening up of 'dead spaces' in the tissues, the removal of contaminated foreign bodies, the trimming of the walls of the wound cavity (to provide a surface of healthy tissues), the relief of fascial tension and the provision of free drainage, with the conservation of as much skin and viable bone as possible. World-wide experience in the War of 1939–45 made it clear that the chemoprophylaxis of wound infection by the administration of sulphonamides, penicillin or other drugs is at best of secondary importance to early surgical treatment, and the latter should never be unnecessarily delayed because such drugs have been used; nevertheless, it became evident in the latter part of the war that penicillin could be very valuable in restraining the development of wound infection in circumstances where early surgical treatment was impracticable.

A point of great significance in wound treatment, which was brought out by research in the War of 1939–45 in extension of studies begun in

that of 1914–18, was the risk of 'hospital infection' of the open wound or burn, and the need to take strict measures to prevent it. Although, as already indicated, bacteria causing wound infection might be introduced into the body at the time of injury, research showed that the haemolytic streptococci responsible for some of the commoner types of severe wound sepsis much more often reached the exposed tissues later, when the wounds were being dressed after the primary operation. These organisms might be carried in the throats and noses of healthy people and they were easily conveyed to the surface of a wound by the contact of soiled fingers, instruments or dressings, by infected droplets from the mouths and noses of those nearby when dressings were removed, or by the dust in the air of a ward. An extensive programme of research on the problem of wound infection acquired in hospital—and on methods of dealing with it—was initiated by the War Wounds Committee in the early autumn of 1940, when the hospitals of the Emergency Medical Services contained not only many wounded patients from France but also large numbers of civilians injured in air-raids on this country (Miles, Schwabacher, Cunliffe, Ross, Spooner, Pilcher and Wright, 1940; van den Ende, Lush and Edward, 1940; Spooner, 1941; McKissock, Wright and Miles, 1941; van den Ende and Spooner, 1941; van den Ende and Thomas, 1941; van den Ende, Edward and Lush, 1941). These co-ordinated studies demonstrated that a large proportion of streptococcal and other wound infections was avoidable if rigid hygienic precautions were taken during the first few weeks of the treatment of wounded or burned patients, but that the prevention of such infections demanded a very strict discipline in the performance of dressings. Recommendations to this effect formed the subject of a memorandum prepared under the joint authority of the War Wounds Committee and the Committee of London Sector Pathologists (Medical Research Council, 1941); the same Committee sponsored the preparation of a set of rules for aseptic dressing technique which was widely distributed by the Service and civilian health departments to hospitals in Great Britain and overseas.

Investigations into the sources of the bacteria causing sepsis in wounds and burns were later extended in two special Research Units set up by the Medical Research Council at the Birmingham Accident Hospital in 1942 and 1944 respectively (see also Chapter 6). The Burns Unit gave special attention to the value of air-purification (air conditioning) as a means of preventing cross-infection in rooms for dressing burns and other open injuries (Bourdillon and Colebrook, 1946), while the Wound Infection Research Unit studied the origin, course and treatment of infection in those common types of minor industrial injury which do not menace life but cause great loss of productive capacity. In confirmation of the earlier observations on war wounds, it was found that streptococcal invasion was usually a late

complication, in the few cases in which it occurred, and it almost invariably resulted from cross-infection. On the other hand, staphylococcal sepsis, which in these small wounds was numerically far more important than streptococcal, commonly rose from invasion by staphylococci that had been carried, hitherto harmlessly, in the nose or on the skin of the patient himself. For the prevention of this form of sepsis, a rigid aseptic dressing technique was itself insufficient, and the repeated application of bacteriostatic drugs was found necessary (Williams and Miles with Clayton-Cooper and Moss, 1949).

The intensive attack on the problem of wound infection in hospitals began in the autumn of 1940 as already mentioned. It had, however, been realised by surgeons from earlier experience that, to minimise the risk of added infection, wounds should be kept securely covered after the primary operation, and should be dressed as infrequently as possible; the importance of immobilisation in the treatment of limb injuries was also appreciated. Since primary suture of battle wounds, immediately after the initial operation, was unsafe, alternative methods had to be found to protect wounds from environmental contamination. The method favoured for this purpose during the campaign in France and Flanders in 1940 was the 'closed plaster' treatment, as used during the Civil War in Spain, though its history is of much earlier origin. Immediately after the operation of wound excision, the injured extremity (with or without a compound fracture) was enclosed in a skin-tight plaster-of-Paris splint for the patient's transport to a base hospital; the plaster was left undisturbed for periods up to several weeks, unless there were clinical indications for removing or changing it earlier. This method was, on the whole, well suited to the conditions of that particular campaign, with its lengthy and difficult lines of evacuation; it had the advantages of protecting the wound from air-borne contamination, of securing good immobilisation, and of discouraging unnecessary re-dressing, but it also had serious disadvantages. The first of these was that, unless the plaster was very carefully applied and the patient carefully observed thereafter, there was risk of interference with the blood supply to the limb, and of the development of gas gangrene or other dangerous infection inside the casing; this risk proved sufficiently great to lead subsequently to a prohibition of the use of closed unpadded plasters for the treatment of British wounded in the field. A less serious but still objectionable feature of the closed plaster treatment, as widely used in 1940, was the offensive smell commonly associated with the soaking of wound discharge through the plaster casing; one method of overcoming this, devised with the help of the Chemical Defence Research Department (Ministry of Supply) and of the Wool Industries Research Association, was to enclose the limb and plaster in a bag of cloth impregnated with charcoal as used in gas-masks (Seddon and Florey, 1942); clinical trials

organised by the War Wounds Committee confirmed the usefulness of this procedure.

The action of the sulphonamide drugs against streptococcal and other infections had been established well before the war, and it was logical to try these drugs for the control of wound infections. Dr. Leonard Colebrook, of the staff of the Medical Research Council, had been appointed Consultant Bacteriologist to the Army in 1939, to direct field investigations on these lines. Treatment with sulphonamides by the mouth was at first contemplated, but reports by Jensen and his colleagues in America (on compound fractures treated in civil practice), and the experiments of Legroux at the Institût Pasteur in Paris, soon made it clear that the local application of the drugs was also likely to have an important effect. With the help of Professor Legroux and Dr. Tréfouël, who had already initiated an active programme of research on wound treatment in the French armies defending the Maginot Line, plans were quickly made for a similar trial in units of the British Army—and for the follow-up of the wounded men so treated. The field studies of Colebrook and his fellow workers in France were supplemented by laboratory experiments by Hawking and others in the United Kingdom. Conditions in the Campaign of 1940 were unfavourable to the routine field application of a new form of treatment, and only a small proportion of the wounded brought back to Britain in that year had received sulphonamide prophylaxis. From the point of view of general military surgery, therefore, that period has been described as the 'pre-sulphonamide era'; it was a period when local sepsis was rife and spreading or generalised infections relatively common.

Further attempts to assess the value of sulphonamides in the prevention and treatment of infection in wounds treated in 'closed plasters' or otherwise were made subsequently in Britain, particularly during the period of intensive air-raids in 1940–1. These observations on air-raid casualties suffered scientifically from the disadvantage that it naturally was not considered ethically justifiable to withhold from such patients any method of treatment which might improve their chances of recovery; there was thus great difficulty in securing adequate control groups. Nevertheless, the impression was gained in these studies that sulphonamides given by mouth or applied locally were of value at least in preventing the systemic spread of local wound infections; and that impression was endorsed by subsequent experience in the field. One carefully controlled small-scale inquiry, made for the War Wounds Committee at Oxford, showed that a single local application of sulphanilamide to severe limb injuries at the time of early surgical excision, and before they were enclosed in 'complete plasters', caused a prolonged selective reduction of the wound flora, but had no demonstrable clinical effect upon the progress of the cases; nevertheless, haemolytic

streptococci, if present at the time of operation, were usually eliminated by the drug (Orr-Ewing, Scott and Gardner, 1941; Orr-Ewing, Scott, Masina, Trueta and Gardner, 1944). These observations on severe limb injuries indicated a rather more favourable effect from a single application of a bacteriostatic agent than that later recorded in minor industrial injuries at the Wound Infection Research Unit at the Birmingham Accident Hospital; repeated applications of sulphathiazole-proflavine powder were here found more useful (Williams and Miles with Clayton-Cooper and Moss, 1949).

Meanwhile, investigations in a Plastic Surgery Unit in England had clearly demonstrated that the local application of sulphanilamide powder or cream to superficial wounds infected with haemolytic streptococci generally resulted in the elimination of those microbes within five or six days (Colebrook and Francis, 1941). In the course of these observations, however, cases were encountered of cross-infection by haemolytic streptococci that were resistant to the action of sulphonamides (Francis, 1942); during the same studies it was noted that another biological variant of the group A haemolytic streptococcus, namely, a non-haemolytic form, was sometimes responsible for septic infections and might easily be missed on account of its failure to haemolyse blood in the ordinary laboratory media (Colebrook, Elliott, Maxted, Morley and Mortell, 1942).

At various times from 1940 onwards, the War Wounds Committee reviewed the existing state of knowledge of the uses and limitations of sulphonamides in wound treatment, and drafted instructions for the guidance of the Service Departments. The latest recommendations approved by the Committee under this heading are incorporated in the second (1945) edition of an *M.R.C. War Memorandum* on the medical use of sulphonamides (Medical Research Council, 1945).

In the period of the North African campaigns, 1941–3, sulphonamides, given locally or systemically, or both, were extensively used in the treatment of the wounded, and some notable modifications in the early surgical treatment of limb injuries were adopted, excision and 'closed plaster' being replaced by excision with drainage, followed by immobilisation in padded and split plaster cases, such as the 'Tobruk splint'. In this 'sulphonamide era' of wound treatment, local sepsis continued to be common, but severe generalised infections became much more rare, even under unfavourable conditions of evacuation.

Early in 1943 a team of investigators was sent by the War Office to North Africa, to examine the possibility of using penicillin for the prevention and control of wound infections in the field. This very important pioneer work, in which Sir Howard Florey and Brigadier (later Sir) Hugh Cairns took a leading part, is described in greater detail in Chapter 7. In its subsequent developments in Italy and

elsewhere it led to a revolution in wound treatment. Once penicillin became generally available it tended more and more to replace the sulphonamides for the prophylaxis and treatment of wound infections.

During the campaign in Italy which began in 1943, a fundamental change in the surgical treatment of limb injuries became practicable, owing to the relatively short lines of evacuation, and the protection against serious infection given by penicillin. This was a reversion to the 'two-stage' operation of wound closure, which had been used with considerable success in 1918, though, of course, without the helpful accompaniment of effective chemotherapy. In this procedure, the primary excision of the wounds, and their closure (usually) three to five days later, were regarded as the two stages of one process. The results of this method of treating wounds were very satisfactory, and it was brought into general use during the later stages of the war on all fronts.

The arrangements made by the Army Medical Department in preparation for the invasion of Normandy in 1944, included an instruction that patients with severe wounds were to receive intramuscular injections of penicillin at regular intervals during their evacuation to hospitals in the United Kingdom; this was thought likely to be specially useful in cases where adequate surgical treatment could not be given before the patient began his cross-Channel journey. A special yellow label was attached to wounded men so treated; it served as a reminder to medical officers to maintain the course of injections, recorded the doses of penicillin (and of other drugs) given, and was later used in analyses by the Army Statistical Department of the effects of the treatment. While the inevitable absence of control series of untreated patients with comparable wounds made it difficult to state with certainty that penicillin was responsible for the remarkably low incidence of severe infection in the wounded men receiving it, few of those who had to deal with the injured had any doubt that this was so; and the favourable opinion of penicillin prophylaxis then formed on clinical impressions was later borne out by the Army's statistical analyses of the recovery rates after severe wounding. As a guide to the use of penicillin in wounds of different types, a pamphlet, based on earlier experience with the antibiotic, had been prepared by the Penicillin Clinical Trials Committee of the Medical Research Council in advance of 'D' day (Medical Research Council, 1944). Numerous reports by individual investigators on the uses of penicillin in wounds of different kinds among the casualties from Normandy were subsequently published in the medical press.

An effort was made during the invasion of Normandy to obtain bacteriological histories of severe wounds from the moment of infliction to the time of healing, with a view to determining the bearing of the initial contaminating flora of the wound, the circumstances of its

infliction, and its immediate and later treatment, upon the liability to sepsis and gas gangrene. To this end arrangements were made for collecting wound swabs taken on the Normandy beaches and seaboard and at various stages during the transport of the wounded to British hospitals, as well as in the hospitals themselves. These swabs were distributed to a number of pathological laboratories for examination. Unfortunately, the lines of evacuation to base hospitals were so various that relatively few of the wounded selected in the battle area for this study reached hospitals where the complete follow-up bacteriological studies could be carried out, and the small number of full bacteriological histories obtained did not add materially to knowledge. What did emerge from the extensive bacteriological work done on the early swabs was the great variety of organisms, both aerobic and anaerobic, contaminating the wounds on infliction; the flora included the classical microbial causes of gas gangrene, but pathogenic staphylococci and streptococci were rare—a finding which supports the view that pyococcal sepsis of war wounds is usually due to later added infection. Most of the organisms found in the early cultures were rapidly eliminated by the combination of surgical treatment, penicillin and gas gangrene antitoxin which was used in the majority of cases and, as already indicated, cases of gas gangrene were few.

The results of penicillin prophylaxis in the patients evacuated to Britain from Normandy were, indeed, so encouraging that the use of penicillin systemically (and sometimes locally as well) was adopted to an increasing extent for the prevention of wound infection in the British Liberation Army, after facilities for early primary operation, and the 'two-stage' wound closure, had been established on the Continent. The remarkable benefits obtained with penicillin in wounds and other conditions during the final Campaign in Europe are described in the book *Penicillin Therapy and Control* published by 21 Army Group (1945). In the middle and later phases of this campaign the organisation of forward surgery, penicillin therapy, evacuation, and base surgery was co-ordinated to allow the closure of 90 per cent. of wounds within a week of their infliction; generalised infections from wounds became extremely rare and local infections were reduced to 'quite small proportions'; statistics show that the wounded man in 21 Army Group had more than a nine-to-one chance of living once he reached surgical aid—a record of success in wound treatment never before achieved in military surgery, and one for which penicillin must undoubtedly be given a large share of the credit.

For a summary of the existing state of knowledge at the end of the war regarding the respective values of the sulphonamide drugs and penicillin in the prevention and treatment of wound infection, reference may be made to the Report of the Medical Research Council for 1939–45, pp. 36–37.

### THE BIOLOGIST'S CONTRIBUTION TO WOUND TREATMENT

From the beginning of the war there was a natural tendency for laboratory research workers, normally engaged in fundamental investigations in one or other of the biological sciences, to divert their attention to practical problems of war surgery, more particularly to the physiology of wound healing. That the experimental biologist had an important contribution to make in this field, at a time when his medically qualified colleagues were largely pre-occupied with the care of patients, formed part of the thesis of *Science in War*, a 'Penguin Special' published anonymously in 1940. It was not surprising, therefore, that, soon after the start of the fighting in Europe, the Medical Research Council received numerous requests from biologists wishing to be put in touch with clinicians with whom they might usefully co-operate in studying wound problems. It was accordingly agreed that one of the earliest functions of the War Wounds Committee should be to make a comprehensive survey of relevant laboratory investigations in progress in Great Britain, and to arrange a conference at which the research workers concerned could meet surgeons and pathologists in the Fighting Services and the Emergency Medical Services, so as to exchange ideas. The survey was undertaken by Professor H. W. Florey and Professor J. Paterson Ross, and on the basis of their report the Medical Research Council invited over a hundred laboratory workers and clinicians to meet in conference at the London School of Hygiene and Tropical Medicine on November 29, 1940. An account of the proceedings of this conference was published in the *Bulletin of War Medicine*, 1941, **i**, 129–136.

It is certain that much valuable co-operation between laboratory workers and clinicians resulted from the conference, and that laboratory methods originally devised for other purposes were in several instances successfully adapted to researches on practical problems of wound treatment. Among the more interesting of the investigations directly arising from the conference, or influenced by it, were the studies by P. B. Medawar at Oxford of the behaviour of skin homografts (Medawar, 1943, 1944, 1945 *bis*), his experiments with J. Z. Young on the use of a strong solution of fibrinogen in natural plasma as a 'glue' for joining the ends of cut nerves (Young and Medawar, 1940), and the work in which he collaborated with E. N. Willmer, of Cambridge, and F. Jacoby, of Birmingham, upon the effects of sulphonamides and amino-acridines on cells growing in tissue culture (Jacoby, Medawar and Willmer, 1941); later Medawar and Jacoby examined penicillin in the same way, and were able to endorse the opinion of Florey and his colleagues that there was a very satisfactory gap between the concentration of this substance which produced bacterial inhibition and that which caused damage to tissue cells.

Similar studies of several other antibacterial agents, including cetyltrimethylammonium bromide, which had been recommended for the cleansing of burns, were subsequently made at Birmingham (Jacoby, 1943, 1945, 1946).

An extensive programme of experimental work bearing on practical problems of war surgery was carried out by Honor B. Fell and her colleagues at the Strangeways Research Laboratory, Cambridge. Dr. Fell collaborated with J. F. Danielli, of the School of Biochemistry, Cambridge, in examining the distribution of alkaline phosphatase in healing wounds (Fell and Danielli, 1943, 1944). Investigations at the Strangeways Research Laboratory also included work on the pathology of keloid scars (Glücksmann, 1944) and, earlier, a clear experimental demonstration that the use of embryonic extracts and certain other substances, reputed, when applied locally, to accelerate the healing of wounds and burns, was unnecessary and undesirable (Dann, Glücksmann and Tansley, 1941 *bis*, 1942).

Further examples of the effective experimental study of problems of clinical interest were provided by Hawking's work at the National Institute for Medical Research on the prevention and treatment of wound infection by the local application of sulphonamides (see Chapter 7), J. Z. Young's researches on nerve grafting, which are described more fully under the healing of nerve injuries below; and the observations of H. E. Hutchison, working under Professor D. F. Cappell, then of Dundee, on the resistance of granulation tissue to the absorption of tetanus and other toxins. The possibility of vitamin-C deficiency being a cause of the delayed healing of wounds was discussed by several contributors to the 1940 Conference, and much work was subsequently done on the subject (see list of publications at the end of this chapter). Progress reports on a number of the studies initiated at this meeting were given at the 55th Conference of the Society for Experimental Biology, held at Cambridge in September 1943, where newer work on the pathology and systemic effects of burns, and some of the earliest trials of penicillin in wound infections, were also described (*Bulletin of War Medicine*, 1944, **4**, 251–257).

In parallel with the early clinical trials of sulphonamide drugs for the prevention and treatment of wound infection, the effects of applying these substances locally to normal and injured tissues was tested experimentally at various centres. The reactions of tissues to the amino-acridine drugs, some of which had been introduced as wound antiseptics in the War of 1914–18, were also intensively examined, special attention being given to the effects of proflavine. While the conclusions of the various observers differed in detail, it was generally agreed that sulphanilamide and sulphathiazole did relatively little damage to the tissues unless they were applied in excessive quantity, when the latter, by reason of its low solubility, might form undesirable

concretions in a wound; its peculiar property of inducing epileptiform convulsions when applied to brain tissue (as described under the heading of Brain Injuries below) also limited its field of usefulness. The same limitation did not apply to sulphanilamide, and this remained an approved local application to battle wounds in the British Services till the end of the war, though the U.S. authorities abandoned it earlier in favour of systemic chemotherapy.

As regards the place of proflavine and similar compounds in wound treatment, there was a wide divergence of opinion between different investigators, though it was agreed that these substances are much more toxic than the sulphonamides to tissue cells, and very much more so than penicillin. Nevertheless, the experience of a number of clinicians indicated that proflavine, especially when used as a powder diluted 1:100 with sulphathiazole as recommended by McIntosh and Selbie, was of value in the disinfection of a dirty wound in which tissue damage caused by the missile, or by established infection, was already severe.

### EMERGENCY AMPUTATIONS

In the summer of 1940 there was considerable argument among surgeons on the subject of 'guillotine' amputations, some contending that they should not be done in any circumstances, others maintaining that when performed for the proper indications, and followed by adequate skin-traction, they had certain limited but noteworthy advantages. With the aim of clarifying the issue, the War Wounds Committee appointed a sub-committee of general and orthopaedic surgeons to consider the whole question of limb amputations for war surgery. No new research was called for in this instance, but the sub-committee was able to give authoritative advice in the subject, for the guidance of medical officers in the Services. The agreed recommendations were published as an *M.R.C. War Memorandum* (Medical Research Council, 1941).

Experience showed that, as the war progressed, guillotine or other circular amputations were less and less frequently resorted to, since it was generally possible to make skin-flaps, and severe infections of the types which may demand urgent primary amputation, with the intention of re-amputation later, became progressively rarer with the successful use of chemotherapy.

### HEALING OF WAR FRACTURES

A sub-committee of the War Wounds Committee was appointed in 1942 to co-ordinate new researches on fracture treatment, and to issue instructions regarding the causes and prevention of delayed bone-healing. One of its objects was to consider whether the healing-time of long-bone fractures sustained during the war was as satisfactory as

could be expected on the basis of earlier experience. A careful analysis of a large series of fractures of the shafts of the tibia and femur in aircrew and others indicated that uncomplicated fractures treated by continuous immobilisation in plaster were uniting as quickly as in former years (Watson-Jones and Coltart, 1943); the authors emphasised the risks of the misuse of skeletal traction and the special significance of distraction of the fragments as a cause of delayed union. Memoranda on the causes and prevention of the delayed union of fractures, and on the avoidance of infection around transfixation pins, were published by the sub-committee in the *Bulletin of War Medicine* (Medical Research Council, 1944).

At the request of the War Office the sub-committee undertook to supervise the clinical aspect of work by Captain G. Blum (later Major Blaine), R.A.M.C., on possible applications of plastics in bone-surgery (Blum, 1944, 1945; Blaine, 1947). Other parts of the sub-committee's research programme were concerned with attempts to find new alloys for use in bone-plating, and to improve the design of the screws used for this purpose. In connexion with these investigations an extensive scheme of collaborative research by surgeons, biologists, chemists, metallurgists, engineers and surgical instrument makers was arranged at a series of special conferences; but the resulting studies had not reached the stage of practical application by the end of the war.

### INJURIES TO BLOOD VESSELS

In the spring of 1944, at the request of the War Office, the Medical Research Council appointed a sub-committee of the War Wounds Committee to advise on the treatment of vascular injuries and to co-ordinate work on the subject at the centres for the care of such cases which formed part of the Emergency Medical Services scheme to deal with casualties expected during the invasion of Normandy. This sub-committee sponsored the preparation of memoranda dealing respectively with the early diagnosis and treatment of wounds of the arteries (including the management of the ischaemic limb), and with the treatment of traumatic aneurysm and arteriovenous fistula (Medical Research Council, 1944; Maybury, 1945).

Accounts of the methods used, and the results obtained, both in the early treatment of arterial wounds in the Second World War and in the later treatment of their effects and complications, will be found in the volume of this History dealing with Surgery, and in a review article by Mason Brown (1949). Here it is necessary only to discuss certain relevant studies of a strictly research nature which were carried out or published by British investigators during the period covered.

(i) *The Physiological Effects of Arteriovenous Aneurysms.* The effects of arteriovenous aneurysms upon the blood volume and the blood picture were examined at Edinburgh by Roscoe and Donaldson (1946).

Fifteen patients with arteriovenous aneurysms of durations ranging from nine to forty-eight weeks were examined before operation and four to ten weeks after occlusion of the fistulae. Using the Evans blue dye method and the technique described by Davis (1942), the authors found that the presence of direct communication between the arterial and venous systems tended to produce an increase of blood volume—as suggested earlier by Holman—but that the increase was not constant. In none of the cases were the volumes found before operation sufficiently high to be definitely abnormal, but a post-operative fall in volume occurred in 12 cases. The total circulating haemoglobin was found to be considerably increased in the presence of a fistula, and in some patients the increase was associated with a mild polycythaemia.

Observations upon the cardiac output and the peripheral blood flow in 12 patients with arteriovenous aneurysms were made by workers at the British Postgraduate Medical School, London, using the technique of cardiac catheterisation and the venous occlusion plethysmograph. In collaborative studies with colleagues elsewhere they found that cardiac output was increased up to 2½ times the normal with large arteriovenous aneurysms, and that the degree of increase had some relationship to the size of the fistula; right auricular pressure and heart rate were moderately increased. Closing the fistula by digital compression of the artery proximal to the shunt produced a slowing of the heart rate (Branham phenomenon), an increase in diastolic arterial pressure, a considerable decrease in cardiac output and a small decrease in right auricular pressure. Teleradiograms made before and after operative closure showed a significant decrease in heart size. The blood flow in limbs unaffected by the shunt was within normal limits when the fistula was open and showed considerable increase immediately it was closed; the increase was much reduced by procaine block of the mixed nerves to the limb (2 cases), suggesting that the increased flow was mainly due to reflex vasodilatation and only in part to the rise in mean blood pressure. The blood flow in the affected limb distal to the arteriovenous fistula was reduced in lesions up to two years (2 cases), normal in a lesion of five years and conspicuously above normal in a lesion of twenty-nine years' duration. In the early cases the negligible blood flow after compression of the artery proximal to the fistula suggested that most of the blood entering the distal part of the limb traversed the aneurysm, while an increased flow in the one long-standing case studied indicated a considerable development of collateral vessels in excess of that required simply for 'compensation'. Resting blood flow in a limb one month after quadruple ligature and excision of the aneurysm (left femoral artery and vein) was the same as in the normal contra-lateral limb and the vascular responses to the raising of body temperature were identical (Cohen, Edholm, Howarth, McMichael and Sharpey-Schafer, 1948).

(ii) *Muscle Ischaemia.* The pathology of Volkmann's ischaemic contracture was investigated by Griffiths (1940). He showed that the histological picture was that of muscle infarction with the formation of muscle sequestra, and he pointed out that Volkmann's contracture could follow embolism of peripheral arteries as well as fractures. Griffiths found that in order to produce muscle infarction experimentally in rabbits it was necessary to ligate not only the main artery but also the collaterals.

The vascular patterns within voluntary muscle were extensively studied in the Department of Human Anatomy at Oxford (Le Gros Clark and Blomfield, 1945; Blomfield, 1945; Le Gros Clark, 1945, 1946). Brief reference to the bearing of this work on the pathology and surgical treatment of gas gangrene has been made under the heading of Anaerobic Wound Infections above. It was shown that in the rabbit the limb muscles were each usually supplied by several arteries with an arcade of anastomoses between them, but that these anastomoses, though apparently free, might in fact be insufficient to prevent partial ischaemia after obstruction of one of the arteries. For example, the tibialis anterior received two main vessels of supply from a common trunk which was derived from the anterior tibial artery; if the lower vessel was tied, the lower half of the muscle immediately became devascularised, so far as functional efficiency of the capillary circulation was concerned, as could be shown by its remaining unstained after an intravenous injection of the dye bromo-phenol blue. Revascularisation of the lower half did not occur for about a week. If the two main vessels to the tibialis anterior were tied, complete revascularisation was delayed for almost a fortnight. Histologically, the ischaemic muscle showed necrosis. The authors found that a remarkable degree of regeneration of muscle occurred within a few weeks of the initial ischaemia following ligation of both arteries to tibialis anterior in the rabbit; the regeneration was effected by a down-growth of fibres from surviving muscle, the fibres appearing to 'flow' down endomysial sheaths or tubes, newly formed by fibroblasts around the dead muscle fibres, the contractile substance of which was in process of removal by histiocytes. The rate of regeneration was found to be at least 1 to 1·5 mm. per day; cross striations appeared by the sixth day, and at the end of three months the individual fibres were of normal thickness.

In man, Blomfield (1945) found, by post-mortem injection of a barium sulphate and collodion mixture into main arteries, that there were five main vascular patterns in the muscles of the limbs:

(1) A longitudinal anastomotic chain formed by a succession of separate nutrient vessels entering the muscle throughout most of its length, as in soleus and peroneus longus;

(2) A longitudinal pattern of vessels derived from a single group of arteries which arose from a common stem and entered one end of the muscle, as in gastrocnemius;

(3) A radiating pattern of collaterals which arose from a single vessel entering the middle part of the muscle, as in biceps brachii;

(4) A pattern formed by a series of anastomotic loops ranging throughout the length of the muscle and derived from a succession of entering vessels, as in tibialis anterior, extensor longus digitorum and the long flexors of the leg;

(5) An open quadrilateral pattern with sparse anastomotic connexions, as in extensor longus hallucis.

The clinical significance of Blomfield's findings was demonstrated by Wood Power (1945), as has already been mentioned. He analysed a series of cases of gas gangrene in which missiles had severed individual arterial branches to muscles, leading to ischaemia of the muscle, or part of a muscle, supplied. Among the cases examined was one of gas gangrene of the arm affecting only biceps brachii, the solitary artery to this muscle having been divided (Pattern 3 in Blomfield's categories). Power pointed out, however, that in general there is much better anastomosis between the major vessels in the arm than in the leg, which is probably one of the reasons for the much lower incidence of gas gangrene in the upper extremity.

### IMMERSION LIMB (PERIPHERAL VASONEUROPATHY AFTER CHILLING)

Since this condition was first fully investigated during the Second World War, it is discussed here in somewhat greater detail than are most of the other subjects of research of which accounts have been published elsewhere. It follows prolonged exposure to degrees of cold insufficient to cause frostbite, and is most often seen in survivors of shipwreck whose limbs have been immersed in cold sea water, though it may occur in others whose limbs have been exposed to prolonged chilling with or without immersion. In aetiology and pathology it is essentially similar to Trench Foot. Experimental work by Lewis (1941, 1942) and others has shown that the prolonged exposure of limbs to temperatures below 18° C. is harmful to the tissues, but the mechanism by which the damage to different structures is caused has been much debated.

Immersion limb was defined and studied in detail by Ungley and others (Ungley and Blackwood, 1942; Ungley 1943; Ungley, Channell and Richards, 1945). During exposure the extremities become numb and swell to a greater or less degree. After rescue three stages may be observed: (i) *the pre-hyperaemic stage*, which is a direct continuation of the events occurring during exposure: the affected limbs remain cold and are pale, blue or mottled, with sensory loss of sock or glove

type and with absent pulses; this stage may last from two to twenty-four hours and is followed, usually suddenly, by (ii) *the hyperaemic stage*: the limbs become hot, red, and increasingly painful and oedematous; blisters may appear and, in severe cases, patches of gangrene; the pulses are full and there are disturbances of sensory, motor and autonomic function; the duration of this stage may vary from a few days to several months; it gradually changes to (iii) *the post-hyperaemic stage*: oedema subsides, vasomotor tone recovers and the skin temperature falls, but the vessels of the limb may become hypersensitive to cold; the cold sensitivity is associated with hyperhidrosis and often with a recurrence of pain and oedema when the patient walks. These sequels may persist for a long time and cause serious disability.

Ungley classified the clinical condition into four grades of severity:—

(*a*) Minimal cases without interference (or with only transient interference) with nerve function. In these patients swelling disappeared within a week and usually there were no sequels.

(*b*) Mild cases with reversible nerve damage. Blisters and gangrene did not appear, oedema usually subsided within three weeks and hyperaemia within seven weeks. The average stay in hospital was six to eight weeks. Later, about one-third of the patients complained of excessive sweating of the feet and about one-sixth of undue sensitivity to cold.

(*c*) Moderately severe cases with irreversible nerve lesions. The neurological abnormalities were more pronounced, and while the oedema might last only three weeks, the hyperaemic stage was prolonged for from six to fourteen weeks. Sensory and motor disturbances persisted for many months.

(*d*) Very severe cases with irreversible nerve lesions, usually with gangrene. Oedema lasted for about three weeks, hyperaemia for as long as four months. Neurological examination indicated still grosser paralysis of sensory, motor and vasomotor activity. Gangrene was invariable, occasionally to the extent of the whole forefoot.

It is important to differentiate immersion limb from frostbite, in which the tissues become frozen, and from the peripheral oedema which may follow starvation and dehydration in survivors who have been immersed for long periods in warmer sea water.

Pathological studies of immersion limb have been made by Blackwood and Russell (Blackwood and Russell, 1943; Blackwood, 1944). All the tissues of the limb are found to be affected in varying degree, the degenerative changes being most marked peripherally. The nerve fibres initially show scattered Wallerian degeneration; later, regeneration occurs. Damage to muscle is regarded as occurring during the exposure; in the early stages the histological picture is that of Zenker's hyaline necrosis, and later it corresponds to the findings in denervation

and re-innervation. The blood vessels are histologically normal. In bone, some early osteoporosis may be followed by subperiosteal new bone deposition.

In the pathogenesis of the condition, according to Ungley, Channell and Richards (1945), there are two main factors—the direct effect of chilling, and the effect of severe ischaemia relative to the metabolic needs of the tissues. During exposure and the pre-hyperaemic stage, intense vasoconstriction is present, and this is thought to be responsible for the damage to nerves. The authors do not regard starvation, dehydration and vitamin deficiency as significant factors. They conclude that the hyperaemic stage depends initially upon the release in chilled, partially ischaemic tissues of stable katabolites with vasodilator activities, leading to a leakage of plasma through the walls of the minute vessels and to the condition of silting of the red blood cells in the lumen which Kreyberg has described as 'stasis' (see also under Frostbite below); prolonged hyperaemia is accounted for by the absence of vasoconstrictor impulses through the paralysed nerves. A fuller account of the complicated pathology of immersion limb, and of its clinical features, is given in the Surgery Volume of the Official History (Chapter 20).

Hints on the prevention of immersion limb, with emphasis on the importance of keeping the feet as dry as possible in ships' lifeboats, were included in the guide to the preservation of life at sea after shipwreck referred to in Chapter 2 above (Medical Research Council, 1943). Treatment of the established condition may be summarised as follows:

(1) *Pre-hyperaemic Stage.*—The patient should not be allowed to walk; his body should be kept warm, but the affected limbs should be kept cool (environmental temperature 15°–18° C.); they should be elevated above heart level. Greene (1942) advocated that the limbs should be kept cold (at 2°–5° C.).

(2) *Hyperaemic Stage.*—The limbs should be exposed to an air temperature of 15°–18° C., cooling being reinforced by a current of air blown from a fan. If a fan is not available, satisfactory cooling may be achieved by nursing the patient prone, with his feet elevated beside an open window (Learmonth, 1943). Cold therapy by ice bags, or in a refrigeration cabinet (Greene, 1942), may help to relieve pain and reduce metabolism, but the skin temperature should not be allowed to fall below 21° C. Sedatives and analgesics may be necessary, and great care should be taken to avoid skin sepsis.

(3) *Post-hyperaemic Stage and Later.*—General measures to prevent flat foot are adopted, and the limbs should be kept warmly clothed. In the treatment of the late cold-sensitive state and of hyperhidrosis, preganglionic sympathectomy may be of value (Telford, 1943). In the more severe cases, amputation at varying levels may be required for gangrene or intractable pain.

### FROSTBITE

Brief reference has been made in Chapter 2 to the cases of frostbite which occurred among passengers flying the Atlantic in aircraft of which the heating and oxygen installations were inadequate. Frostbite was also a hazard in the naval convoys proceeding to Arctic ports, but by suitable precautions—including the wearing of special cold-weather clothing—the risk was minimised, and there was little opportunity for clinical research on the subject by British investigators during the war.

Experimental work on the pathology of frostbite was carried out in England by Greene (1941, 1943). He showed that freezing to solidification did not of necessity lead to necrosis, and he concluded that the view of Lewis that gangrene in frostbite was due to mechanical damage to the cells by ice crystals was untenable; like Lewis and Love, he found little if any evidence of thrombosis in tissues exposed to dry cold. Greene's findings confirmed the studies made earlier by Rotnes and Kreyberg in Norway, in demonstrating that the essential lesion in frostbite was an increased permeability of small vessels, as a result of which there was excessive transudation of fluid into the surrounding tissues. When this process occurred with great severity, the affected vessels became 'silted up' with stranded erythrocytes and leucocytes. These clumps of particulate cells (which might ultimately become organised) cut off the blood supply from distal tissues and were thus indirectly the cause of gangrene.

### THE TREATMENT OF BURNS

(*a*) *Heat Burns*. The Medical Research Council sponsored an extensive programme of research on the pathology and treatment of burns during the war. An informal co-ordinating team, to assess the results of current methods of treatment, was set up in 1940 under the authority of the War Wounds Committee. Soon after the start of the air war, evidence was forthcoming that coagulation by tannic acid, hitherto widely recommended, was unsuitable for treating the typical aviator's burns, involving the face and hands; it prevented the early movement of the eyelids and fingers which is so important in the care of these injuries, and, if associated with infection beneath the eschar, was apt to lead to scarring, deformity, or even, through interference with the blood supply, to gangrene of the finger tips. Later, the tannic acid treatment of deep or extensive burns was found to have other dangers, particularly a tendency to cause liver damage, and its use for any type of burns was practically abandoned in British Service and civilian practice. The risk of liver damage from the absorption of tannic acid applied to burns was pointed out in 1942 by W. C. Wilson in an unpublished report to the War Office; it was confirmed in experiments in the United Kingdom by Barnes and Rossiter (1943) and Cameron,

Milton and Allen (1943), as well as by independent investigators in Canada and the United States.

The rejection of tannic acid as a treatment for war burns naturally led to many studies, both under official auspices and by individual workers, which had the object of finding satisfactory alternatives. To this end, a small Burns Research Unit was established by the Medical Research Council at the Radcliffe Infirmary, Oxford, in 1941. Work done here included tests of the envelope irrigation treatment with sodium hypochlorite recommended by Bunyan (1940, 1941), and an examination of the value and safety of using 'closed plaster' combined with postural drainage for treating burns of the limbs (Barnes, 1943). Although good results were obtained with the closed plaster method under the carefully controlled conditions of its application at Oxford, it was considered by many surgeons to involve too many hazards for general use in war burns; in particular, like the tannic acid treatment, it prevented early movement of the joints and tendons. In the special centres set up by the Royal Air Force and the civilian Emergency Medical Services for the treatment of burns in aviators and others, chief reliance (until the advent of penicillin treatment) was therefore placed upon the local use of sulphonamides together with saline baths; the sulphonamide powder or cream was applied between the baths, under soft paraffin mesh, the hands being elevated on light splints in the 'basic functional position'; the danger of a toxic degree of absorption of sulphonamides from the damaged area into the blood-stream, shown subsequently to occur with extensive burns, did not apply in the same degree to burns of limited extent, such as those of the hands. With this and other methods of local treatment it was accepted as axiomatic that the control of shock by the intravenous administration of plasma or whole blood was of major importance, and that skin-grafting should be done as early as possible.

Part of the programme of the Unit at Oxford was concerned with testing the value of synthetic detergents for cleansing and disinfecting burns and the surrounding skin; the substances examined included cetyltrimethylammonium bromide (now known as cetrimide). Following a favourable report by Barnes (1942), and confirmatory work at other centres, cetrimide was widely used for this and many other purposes in surgical practice.

It soon became evident that the problems connected with the pathology and treatment of burns and their systemic effects were sufficiently numerous and complicated to demand attack on a wider front. A Burns Sub-committee of the War Wounds Committee was accordingly appointed in 1942, to organise a co-ordinated scheme of laboratory and clinical investigations; it included representatives of each of the Fighting Services, the Ministry of Health, the Department of Health for Scotland, the Ministry of Home Security and the Ministry of Supply;

among those serving upon it were the surgeons in charge of several of the centres for the treatment of burns and maxillo-facial injuries in Britain; this provided useful co-operation and co-ordination in the clinical trial of new methods of treatment. Prominent among the researches carried out for the sub-committee were the important series of experimental studies in Professor R. A. Peters's department at Oxford on the problem of 'burns toxaemia' and on the metabolic effects of burning; the investigations undertaken by Professor G. R. Cameron and his team, then working at the Chemical Defence Research Experimental Station of the Ministry of Supply at Porton, on phosphorus burns, on the toxicity of various local applications used for burns, and on the treatment of burns by 'pressure' methods; and the extensive scheme of clinical and bacteriological studies of burns and scalds, directed by Dr. L. Colebrook in the Burns Research Unit which was set up by the Medical Research Council at the Royal Infirmary, Glasgow, in 1942 and transferred in 1944 to the Birmingham Accident Hospital and Rehabilitation Centre. Some of these investigations are noticed in greater detail below.

The much debated problem whether there is a true toxaemia of burns, independent of the toxic effects of tannic acid treatment and of the toxaemia which may be associated with severe bacterial infection, was examined by Peters and his colleagues. Their work started from the hypothesis that enzymes or other substances liberated from tissues damaged but not coagulated by heat, towards the margins of a burn, might themselves act as systemic poisons. At the outset of their studies, they devised a method for producing standard experimental burns at known temperatures, which was used in interesting observations of the microscopic changes in and around skin burns, and in many other investigations of the local and systemic effects of thermal injury (Leach, Peters and Rossiter, 1943). The subsequent developments of this work were too numerous to mention here; they have been reviewed elsewhere by Peters (1945). The finding that a proteinase was among the substances liberated from the skin after burns was thought to have a possible bearing upon the problem of blister-formation in these injuries, though the fact that the blood normally contains an active 'anti-proteinase' made it unlikely that the proteinase was itself capable of producing damage to the internal organs (Beloff and Peters, 1944–45 *bis*, 1946; Beloff, 1946). A substantial part of the research programme of Peters and his colleagues was concerned with the metabolic changes following burns and is discussed later in this chapter, under the heading of the metabolic effects of injury. Work by Rossiter and Peters (1944) on the control of oedema formation after burns in rats, by the application of moderate external pressure, was later extended by Cameron and his colleagues at Porton in investigations with goats. They concluded that pressure applied by means of plaster bandages to experimental

limb burns was of value both in saving life and accelerating healing (Cameron, Allen, Coles and Rutland, 1945, 1946). These findings were of special interest in relation to the increasingly wide adoption, towards the end of the war, of treatment by 'pressure dressings' for burns in man.

Apart from their work on the 'pressure' treatment and their studies of the toxicity of tannic acid, already mentioned, Cameron and his colleagues made experimental observations on the toxicity of gentian violet and of propamidine preparations as currently used for the treatment of burns (Allen, Burgess and Cameron, 1944). They also had a major share in the investigations of the effects and treatment of phosphorus burns, mentioned below.

The studies made by Colebrook and his colleagues in the Burns Research Unit of the Medical Research Council at Glasgow and later at Birmingham were concerned with the prevention and treatment of infection in burns and scalds, and with the control of burns 'shock' by fluid replacement. An important investigation undertaken in the Unit at Glasgow was aimed at devising a simple and efficient 'first-aid' treatment for burns. There is general agreement that all patients with severe or extensive burns should, when possible, be sent to well-equipped hospitals without delay, and without preliminary 'first-aid' treatment of their injuries. There are, however, circumstances, particularly in warfare, in which it is impossible for the burned patient to be taken immediately to hospital. For use in such cases, and in patients with minor burns involving no risk to life, the workers at Glasgow devised a cream of which the active ingredients were sulphanilamide and cetyltrimethylammonium bromide (Colebrook, 1944; Colebrook, Gibson and Todd, 1944; Colebrook, Gibson, Todd, Clark, Brown, Anderson and Semeonoff, 1944). For the local treatment of burns in hospital, Colebrook and his colleagues used initially a sulphonamide cream and subsequently—following the lead of Bodenham (1943)—one containing penicillin as well. This treatment was applied with rigid aseptic precautions, after the control of 'shock' by transfusion; it was combined with the use of pressure dressings, changed infrequently, and was followed by early skin-grafting. Incidental studies in the Unit at Glasgow dealt with the fate of skin homografts in man (Gibson and Medawar, 1943), and with the social factors in accidental burning injuries (Brown, Lewis-Faning and Whittet, 1945). After transfer of the Unit to the Birmingham Accident Hospital special attention was given to the value of air hygiene (air conditioning) as a means of preventing cross-infection in rooms used for dressing burns (Bourdillon and Colebrook, 1946). It was found that the risk of transmitted infection could be greatly reduced by carrying out all dressings in a stream of dust-free, warm air in a room specially reserved for that purpose, and equipped with a special ventilating plant so that the air was constantly

changed. Apart from these extra precautions against transmitted infection, the treatment of the burns remained substantially the same as at Glasgow, except that latterly a penicillin cream without sulphonamide was used, to avoid the risk of skin sensitisation to sulphonamides. That the results obtained, even in very severe burns, by the methods and disciplines practised in the unit at Birmingham were exceptionally good, was demonstrated in a statistical study by probit analysis carried out by Bull and Squire (1949).

It is doubtful whether there is any other subject in medicine about which the opinion of responsible experts differs so widely as on the treatment of burns; this applies particularly to the local condition, but, although there is general agreement on the importance of systemic treatment to control burns 'shock', there is disagreement even here on the respective merits of plasma and whole blood as infusion fluids and on the value of various ancillary measures. In the foregoing account it has been possible to mention only those methods of treatment which were tested under official auspices in the United Kingdom during the war. A general review of the problem of plasma loss in burns was prepared under the authority of the Burns Sub-committee by Rossiter (1943), and a survey of some of the many different local treatments recommended during the war years was published towards the end of hostilities by Green (1945 *bis*). For further information about British work on thermal burns during the war reference may be made to the Surgery Volume of this History, Chapter 7.

(*b*) *Chemical Burns.* Studies of chemical burns, such as those due to war gases, were mainly the concern of the Ministry of Supply and are dealt with in Chapter 10. In research on phosphorus burns, which involve both chemical and heat effects, there was close liaison between the Burns Sub-committee of the Medical Research Council and workers for the Ministry of Supply at Porton. Recommendations on the first-aid treatment of this type of injury, based on work carried out by Cameron and his colleagues at Porton and by Bourdillon at the National Institute for Medical Research, were incorporated by the medical departments of the Fighting Services, and by the Ministry of Health and Ministry of Home Security, in instructions for the care of air-raid casualties.

### MISCELLANEOUS ACTIVITIES OF THE WAR WOUNDS COMMITTEE

Among the miscellaneous activities of the War Wounds Committee was the organisation of the first clinical trials in the United Kingdom of the synthetic analgesic drug now known as pethidine. It was thought that this substance, which had been prepared in Germany before the war, might form a useful substitute for morphine in the event of the supplies of the latter running short. Two reports on the tests organised

for the committee were published (Christie, 1943; Fitzgerald and McArdle, 1943).

At the request of the War Office and the Royal College of Surgeons of England, the Medical Research Council (through a sub-committee of the War Wounds Committee) sponsored arrangements for making a national collection of pathological specimens illustrating the morbid anatomy of wounds, injuries and diseases occurring during the war. Destruction during an air-raid in 1941 of the Army Medical Collection housed in the Royal College of Surgeons, London, made it desirable not only to collect specimens of lesions characteristic of the War of 1939–45, but also so far as possible to replace for teaching purposes the more important of the war specimens amassed in 1914–18. The task of collecting the specimens, and supervising their preparation for display, was undertaken for the Council by Dr. Joan M. Ross and Sir Gordon Gordon-Taylor. At the end of the war the collection was distributed to various institutions, the greater part of it going to the museum of the Royal College of Surgeons in London (Gordon-Taylor, 1949).

An important ancillary to the collection of pathological specimens was the provision, through the generosity of the Metal Box Company Ltd., of the services of Mr. P. G. Hennell and the technical facilities of the firm's photographic department for taking coloured photographs of wounds at different stages of treatment. The high quality of the direct colour photographs taken by Mr. Hennell gives them unique value for purposes of teaching and record. A large selection of the photographs is to be housed permanently in the museum of the Royal College of Surgeons (Gordon-Taylor, 1949). Some of these are reproduced in the Surgical Volume of this series.

## Brain Injuries

A committee, under the chairmanship of Professor E. D. Adrian, was appointed by the Medical Research Council early in 1940 to advise on the promotion of research into the effects and treatment of war injuries involving the brain. It included representatives of the three Fighting Services, the Emergency Medical Services and the Ministry of Pensions, and its membership covered the specialties of medical and surgical neurology, neuropathology, psychology and psychiatry.

One of the first matters to which the committee directed attention was the need for keeping accurate and detailed case-histories of patients with brain injuries, and the arrangements made for this purpose at the special centres which had been established for the treatment of head injuries in Service and civilian patients were carefully examined. The preparation of a series of critical reviews on different aspects of head injury, based on published data, was undertaken by members of the committee and their colleagues, as a preliminary to drawing up plans for further research in this field.

To facilitate the work of the main committee, several sub-committees were formed to deal with different aspects of brain injuries and their effects. Among the problems studied in this way were (*a*) the assessment of the psychological state of patients after head injuries; (*b*) the relationship of head injury to subsequent epilepsy; (*c*) the use of electro-encephalography as an early diagnostic measure in cases of post-traumatic epilepsy; (*d*) the prevention and treatment of headache and other complications following head injury; (*e*) questions relating to the disablement and rehabilitation of patients with brain injuries. Schemes for research at the special head injury centres and elsewhere were formulated by the sub-committees, and arrangements made for the co-ordination and extension of investigations already in progress. In connexion with the work of the sub-committee dealing with the assessment of psychological states after head injury, a glossary of the psychological terms commonly used in recording such cases was published (Medical Research Council, 1941). This sub-committee also undertook the task of drawing up a list of suitable psychological tests for use in the clinical examination of patients with head injuries.

The committee arranged for clinical and experimental studies of brain injuries, their effects and treatment, to be carried out at a number of centres, and for an inquiry to be made into the effects of travel on patients in the acute stage of such injuries; it was concluded that these patients, unless very deeply unconscious, stand travel well, especially before operation, and that their transport from the scene of injury to special centres where they can receive expert neurosurgical attention is therefore advisable. A memorandum on head injuries in air-raid casualties, drawing special attention to the potential dangers of scalp wounds, was prepared for the committee by Professor G. Jefferson and circulated to the Service and other interested Government Departments for the guidance of medical officers; its conclusions were emphasised in a subsequent paper by Botterell and Jefferson (1942).

The programme of research on head injuries in Great Britain in the earlier stages of the war was concerned largely with mechanical factors —including the mechanism of brain damage and the nature of concussion, the problem of pressure, and the role of oedema in closed injuries. Experiments by Denny-Brown and Ritchie Russell, in the Physiological Laboratories at Oxford, confirmed that when force is applied violently to the head, it is the sudden acceleration or deceleration of the head, rather than compression of the brain by indentation (reduction of cranial capacity), which causes mischief, and these workers were able to measure critically the alterations of speed of motion necessary to cause cerebral damage of different degree (Denny-Brown and Russell, 1941); Holbourn's inquiries into the physics of cerebral torques and sheering strains in relation to cerebral injury also contributed to knowledge of the subject (Holbourn, 1943). Concurrently, at several different

neurosurgical centres observations were made upon the lumbar cerebrospinal fluid pressure in head injuries. It was found generally to be little raised if artefracts were avoided. Red cell counts were made to estimate the degree of subarachnoid bleeding in cerebral laceration; very high figures were occasionally reported with recovery of the patient. It is clear that dehydration, so long advocated in America and generally so sceptically regarded in this country, especially in the light of J. G. Greenfield's observations, has no place in the treatment of head injuries where there is no significant rise of pressure or where a rise in pressure is due to gross haemorrhage, though it is valuable when dangerous hypertension is due to local oedema around lacerations or to oedema around thrombotic or infective foci, or for fluid accumulations in ventricles or subarachnoid spaces. McKissock and Paterson carried out continuous measurement for some hours of the effects of hypertonic solutions in lowering cerebrospinal fluid pressure, and found these less effective than many had claimed (Paterson, 1942). Meanwhile, during the air-raids of 1940, Jefferson had been able to show that the incidence of intracranial sepsis following scalp wounds was much reduced when these were treated by specialists at neurosurgical centres; his evidence on the subject (referred to above) led to an official instruction that hospitals should notify their Regional Neurosurgical Advisers of such cases, especially when caused by bombs, and it did much to improve the results of treatment of civilian head injuries.

The large number of motor-cycle dispatch riders who came to grief and suffered depressed fractures of the frontal bones with injuries to the frontal sinuses and lacerations of the dura caused great concern to the Army. Work by Cairns and his colleagues at Oxford resulted in the development of a protective helmet, of which the use was made compulsory by the War Office (Cairns, 1941; Cairns and Holbourn, 1943). The adoption of this helmet quickly led to a decrease in the number and severity of head injuries in motor cyclists; while, in the field of surgical technique, the dural repair operations carried out for fractures of the paranasal sinuses in the victims of such accidents, and for similar injuries incurred in aeroplane crashes, undoubtedly saved many lives. The special Head Injuries Hospital set up by the Army at St. Hugh's College, Oxford, under Brigadier Cairns proved an excellent training ground in brain surgery and gave (under the peculiar conditions of war-time) an unique opportunity for concentrated observation. Close contact was maintained with neurosurgical units sent overseas after training at Oxford, and the early battle experience of P. B. Ascroft's unit in the Middle East gave useful pointers to further research in this country.

Laboratory experiments by Dorothy Russell and others at Oxford provided valuable evidence on the effects of amino-acridine antiseptics and of chemotherapeutic agents (sulphonamides and penicillin) upon

brain tissue, and on the reaction of tissues to acrylic resin plates designed for skull repair (Russell and Falconer, 1940 *bis*, 1941, 1943; Russell and Beck, 1944, 1945; Small and Graham, 1945; Beck, Russell, Small and Graham, 1945).

Investigations on the effects of sulphonamides on brain tissue were made also at the National Hospital, Queen Square, London (Botterell, Carmichael and Cone, 1941) and at Edinburgh (Watt and Alexander, 1942). It was at Edinburgh that the epileptogenic effect of sulphathiazole powder when applied directly to the brain was first noted (Watt and Alexander, *loc. cit.*); this finding, confirmed elsewhere, led to the issue by the Brain Injuries Committee of a warning against the use of sulphathiazole in this way. Later, members of the committee and their co-workers took a leading part in establishing the value of penicillin in the treatment of head wounds. They also co-operated in the clinical trials in this country of fibrin foam, human thrombin and related products as agents to control bleeding.

A gift from the Rockefeller Foundation of three Grass recording instruments made it possible to set up special units for investigating the effect of brain injury upon the electro-encephalogram. Work at Oxford on the medical aspects of head injuries included Denis Williams's studies of electro-encephalographic changes (Williams, 1941 *bis*; Williams and Denny-Brown, 1941), and the investigations of traumatic amnesia, traumatic epilepsy, focal syndromes, and other problems which have been continued by Ritchie Russell since the end of the war as part of a follow-up and social welfare service for patients who have had brain injuries (Ritchie Russell, 1947); a Head Injury Advice Bureau for the benefit of pensioners with brain wounds has been set up in relation to this scheme. At Edinburgh also, special attention has been given to the social aspects of brain injuries. A psychiatrist (Andrew Paterson) and a psychologist (O. L. Zangwill) were added during the war to the team of surgical and medical neurologists, and specially skilled personnel were secured for rehabilitation services—in particular, occupational therapy and speech therapy. With this team fundamental inquiries were made into defects of emotional and cognitive functions and their correspondence to associated specific brain injuries (Zangwill, 1945). The rehabilitation of the patients by methods of re-education and of substitution of impaired functions was explored. The influence of persistent defects upon practical vocational performance and upon adjustment to vocational and other environment were the subject of special studies. While the follow-up investigations must necessarily take several more years to complete, there was already reassuring evidence, when this account was written in 1950, that only a relatively small proportion of those who sustained head injuries are lastingly or seriously affected, that mental incapacities are rare, and that manual skills are only infrequently lost.

## Nerve Injuries

A Nerve Injuries Committee was set up by the Medical Research Council in October 1940, originally as a sub-committee of the Brain Injuries Committee whose work has just been described; its membership, like that of most of the Council's other war-time committees, included both Service officers and civilians. The Chairman, Dr. (later Brigadier) G. Riddoch, was also consultant adviser on nerve injuries to the Emergency Medical Service in England and Wales and consulting neurologist to the Army. In many respects the committee's programme of clinical studies could be regarded as a continuation of that sponsored very effectively during the War of 1914–18 by an expert committee of the (then) Medical Research Committee. At a later stage of the war the committee's terms of reference were extended, like those of its predecessor, to include work on spinal injuries.

The five recognised centres for the care and study of cases of nerve injury in England and Scotland were staffed by civilians so that there could be complete continuity of treatment and supervision irrespective of the status of the patient. Sailors, soldiers, airmen, pensioners and civilians were admitted and dealt with alike. The Ministry of Pensions rendered invaluable service in the follow-up work, with the result that in cases where prolonged observation was necessary continuous records of progress over periods of from three to five years were commonly obtained. The very satisfactory organisation for clinical research thus ensured was closely integrated with the laboratory work carried out by J. Z. Young and his colleagues at Oxford, by Blackwood at Edinburgh and by Doupe at Winwick (Warrington). The schedule of investigations was so lengthy that the work was shared out between the centres with practically no overlapping, though certain clinical researches requiring a large mass of material were carried out in concert.

Ludwig Guttmann (1940) perfected his method for investigating sudomotor activity and used it, along with detailed sensory examination, to chart the wide variations that occur in the distribution of cutaneous sensory nerves. Richards (1943) made a detailed study of the vasomotor changes following nerve injury, his instrument of choice being thermocouples connected to a sensitive galvanometer for measuring skin temperatures. Later Learmonth and he turned their attention to the wider subject of combined neurovascular injuries.

The electrical examination of paralysed muscles engaged the attention of Bauwens (1941) and Ritchie (1944), who agreed that the most useful information could be obtained from the assessment of strength-duration curves. An apparatus delivering square wave impulses of various durations and frequency became available, with the result that a method of examination previously confined to the laboratory became established as a valuable clinical aid in diagnosis and research. In the

same way, electromyography was taken from the laboratory to the clinic by Weddell and his colleagues (Weddell, Feinstein and Pattle, 1943). The role of electrical stimulation in the prevention of atrophy and fibrosis of denervated muscle had long been a matter of dispute. Gutmann and Guttmann (1942) repeated the experiments of earlier workers, with a number of refinements, and showed conclusively that in rabbits, at any rate, the treatment was effective. But no comparable clinical experiments had ever been made until they were carried out by Jackson and Seddon (1945). Comparable cases of ulnar or combined ulnar and median nerve injury were treated over long periods with or without galvanism, the treatment being identical in other respects. By a simple volumetric method it was shown that daily treatment of tolerable duration was effective in arresting though never in reducing muscle atrophy.

The Oxford workers devoted much attention to the phenomena of regeneration, including the rate of advance of the outgrowing axon, and of the processes of maturation that followed. Seddon, Medawar and Smith (1943) devised a method for measuring nerve regeneration in man and were able to show that the rate was not uniform but fell off progressively as the process approached completion.

Various practical surgical problems were also investigated. Zachary and Holmes showed that primary nerve suture, although theoretically ideal, gave unreliable results in clinical practice, owing to the frequency of concomitant interstitial damage of the stumps of the severed nerve and the risk of more or less post-operative separation at the suture line (Zachary and Holmes, 1946). In consequence, secondary suture emerged as the treatment of choice, a necessary feature of the operation being adequate mobilisation of the stumps. Highet, Holmes and Sanders found that there was a biological limit to the extent of the gap that could safely be closed by this means. Although very large gaps could be closed without difficulty by extensive mobilisation of the nerve and acute flexion of appropriate joints, it was found that however carefully the post-operative stretching was carried out the nerve underwent extensive fibrosis, indistinguishable from that produced by an acute traction lesion and effectively preventing regeneration (Highet and Holmes, 1943; Highet and Sanders, 1943). Thus it was evident that the field for employment of extraordinary methods of nerve repair would be unexpectedly large. Fortunately, by this time Young and his colleagues had completed a very detailed survey of the results of experimental nerve grafting and had arrived at the conclusion that autogenous grafts gave results little, if at all, inferior to end-to-end suture, and homogenous grafts (in rabbits) a fair proportion of successes. Heterogenous grafts were a failure. At Winwick and at Oxford homogenous grafts were used in a small number of otherwise hopeless cases but without success; it was found that the graft provoked a violent

reaction which ended in its destruction or encapsulation, a process which, as Seddon and Holmes (1944) suggested, seemed analogous to the destruction of homogenous skin grafts investigated by Medawar and Gibson. It was likely that the implanted tissue provoked an acquired immune reaction. At Oxford attention then turned to the use of autogenous grafts. An obvious limitation was the quantity of donor nerve tissue available but in the course of five years some 70 cases were grafted, with results at least as good as those obtained after end-to-end suture (Seddon, 1947). Plasma clot suture, first introduced by Young and Medawar (1940) as an experimental procedure in the laboratory, was found to be a valuable aid in cable grafting. In short, there are no biological objections to this form of treatment; the hazards are wholly technical and most of them can be overcome.

In a patient who has had an open wound and who presents evidence of complete paralysis of a nerve, the frequency of division of the nerve is so great—between 50 and 70 per cent.—that it became the established practice always to explore the nerve as soon as local conditions were favourable. Young and his colleagues had shown the harmful effects of delay in the periphery of the divided nerve, in the decline of activity of the Schwann cells at the suture line, and also in denervated muscle (Young, 1942; Holmes and Young, 1942). Subsequent analysis of over 1,000 clinical results, observed over periods of between three and five years, amply confirmed the desirability of early secondary repair. Zachary found that for each nerve at various levels there was a critical period of delay, and that if repair was attempted after this time the prospect of a satisfactory recovery was very remote. These analyses of the results of suture are unique. The various investigators agreed on an objective neurological system of grading of recovery; assessments were made at regular intervals over long periods; the pooled results were collected and analysed by one man, and presented with commendable simplicity and precision. It is intended that an account of this work shall form part of a Special Report of the Medical Research Council dealing with various aspects of the committee's programme.

Reviewing the programme as a whole, it can be said that although no spectacular discoveries were made, the precise documentation of biological phenomena and of the results of operation removed many misconceptions about the morphological anatomy of the peripheral nervous system, and a number of irrational procedures from the surgery of the system. Diagnosis and treatment were placed on a sounder basis.

To assist medical officers to recognise the effects of injury to individual nerves, the committee sponsored the publication of a pamphlet, illustrated by many photographs and diagrams, the material for which had been compiled by the staff of the Department of Surgery at

Edinburgh University and the Peripheral Nerve Injury Centre, Gogarburn, and presented to the committee by Professor J. R. Learmonth (Medical Research Council, 1942, 1943).

### SPINAL INJURIES

As already mentioned, the terms of reference of the Nerve Injuries Committee were subsequently broadened to include also problems relating to spinal injuries. The controversial question of the care of the paralysed bladder was given special consideration, and recommendations on the subject were incorporated in a memorandum on first-aid and early treatment in traumatic paraplegia (Medical Research Council, 1944).

With a view to the eventual use of case records for research purposes, the committee drew up a scheme for note-taking in spinal injuries with neurological complications, details of which, together with a skeleton form for summarising the recorded notes, were circulated to Service and civilian medical officers in charge of patients with spinal injury.

With the co-operation of surgeons working at a number of centres throughout Great Britain, an investigation was made into the value of operative treatment for sciatica caused by prolapsed intervertebral disc. This included a follow-up system for which the administrative machinery already in use for peripheral nerve injuries was employed.

## Systemic Effects of Injury

### TRAUMATIC SHOCK AND RELATED CONDITIONS

During the War of 1914–18, research on wound shock formed a substantial part of the programme of the Medical Research Committee, the predecessors of the Medical Research Council. The characteristics of the syndromes following injury and haemorrhage were studied both in the physiological laboratory and at the bedside, and special observers were sent to France to co-operate with British and American surgeons treating battle casualties in the field. Accounts of the more important investigations were published in three Special Reports of the Medical Research Committee in 1919.

After the armistice in 1918, the urgency of the shock problem declined *pari passu* with opportunities for its large-scale clinical investigation, and, apart from the progressive introduction of blood transfusion methods into routine surgical and medical practice, few significant advances in knowledge of shock and its treatment were made in the years between the wars.

When war broke out again in 1939, the Medical Research Council immediately appointed a committee on Traumatic Shock to direct a resumption of active research on the subject. The committee, which included representatives of the Fighting Services and of the civilian Emergency Medical Services, planned its investigations on two main

lines, namely clinical and haematological studies of blood volume and the effects of blood loss, and the production of wound and burns shock experimentally; when the first wounded arrived for treatment, work was also started on the effects of giving high concentrations of oxygen to patients in shock. In the meantime, it was considered urgently desirable to prepare a concise summary of the existing practical information regarding the treatment of wound shock, for the guidance of medical officers who would have to deal with casualties in the fighting forces and with air-raid casualties in civilians. The committee, in co-operation with the Army Medical Service, accordingly drafted a booklet on the subject, which was published as the first of the *M.R.C. War Memoranda* (Medical Research Council, 1940). In the light of experience gained during the first four years of active warfare, a revised and amplified edition of this was issued in 1944.

In compiling the recommendations put forward in the memorandum, the Committee on Traumatic Shock worked in close touch with the Blood Transfusion Research Committee of the Medical Research Council, and descriptions of the methods and apparatus used for blood transfusion in the Army and for civilian air-raid casualties were given in appendices to the booklet. The Shock Committee also co-operated closely with the War Wounds Committee and its sub-committees, particularly the Burns Sub-committee. A special sub-committee of the Shock Committee advised on problems of anaesthesia for severely injured patients. Another sub-committee (concerned with analytical methods) started a train of investigations which has led to substantial improvements in several analytical procedures for blood constituents, including haemoglobinometry (see Chapter 9). A joint sub-committee of the Shock Committee and the War Wounds Committee co-ordinated the investigations of the incidence and causation of cases of renal failure following crushing injuries in air-raid casualties which are outlined in the next five paragraphs (see also Surgical Volume of this History, Chapter 19).

During the intensive air-raids on London and other cities in 1940–1, a clinical and pathological condition previously unrecognised in Britain became well-known in the hospitals where casualties were treated; it occurred in persons who had been buried for several hours beneath masonry or other heavy debris. In a typical case, the patient, brought to hospital after being pinned down by a limb for three hours or more, showed initially some redness and blistering of the compressed limb, which later swelled. As fluid accumulated in the limb, haemoconcentration occurred and the blood pressure fell. The blood pressure level could usually be restored to normal by plasma infusions, but soon signs of damage to the kidneys appeared, and about a week after injury the patient might die in uraemia, with hypertension and with an increased content of potassium in the blood. These changes, it was

found later, had been partly described by German authors during the War of 1914–18, but they had remained almost unknown elsewhere.

The concept of 'crush injury', as this condition was at first called, arose mainly as the result of observations made by E. G. L. Bywaters and his colleagues at the British Postgraduate Medical School, London. In March 1941, data on some sixteen examples of the syndrome were published; it was noted then that necrosis of muscle was the one pathological feature, apart from the renal changes, which seemed to be common to fatal cases of this type, and that a pigment—afterwards shown to be muscle pigment (myohaemoglobin)—was present in the renal tubules and sometimes in the urine (Bywaters and Beall, 1941; Bywaters, Delory, Rimington and Smiles, 1941).

The incidence of the crush injury syndrome in air-raid casualties has been estimated at between 1 and 5 per cent. Compression by debris following bomb explosions is not, however, the only cause of the condition; it has been found to follow burial after mining accidents, and a similar state was observed in victims of the shelter disaster at an underground railway station in 1943, when the factor responsible for the compression of limbs was not debris but the weight of fallen and impacted human bodies (Bywaters, Crooke and Morris, 1943). Moreover, a condition closely resembling the crush injury syndrome has been shown occasionally to follow fractures and vascular injuries sustained in battle or in civil accidents. Some of the cases of renal failure following injury, seen during the war, were undoubtedly due to treatment with the less soluble sulphonamides or to mismatched blood transfusion, but apart from these and the cases definitely following compression, there was a residue of patients with closed limb injuries in whom ischaemic necrosis of muscle occurred and muscle pigment was demontrated in the urine, just as in the typical cases of crush injury. In view of this, the term 'ischaemic muscle necrosis' has been suggested for the syndrome, so as to include cases where the muscle ischaemia is due to causes other than compression.

During the years 1941–3, much experimental work on this subject was done in the United Kingdom. Barnes and Trueta (1942) found that a widespread and persistent arterial spasm developed in the limbs of rabbits after the release of prolonged compression by tourniquets. Pochin (1942) investigated the oedema which follows obliteration of the blood supply to the skin, and Eggleton, Winton and others, the renal clearances following trauma and ischaemia in animals (Eggleton *et al.*, 1942, 1943; Eggleton, 1944). Studies by Bywaters and his colleagues showed that, in rabbits, prolonged compression of the thigh muscles was followed by oedema of the limb, haemoconcentration and fall in blood pressure; no muscle pigment was detected in the urine (there being no myohaemoglobin in the thigh muscles of the rabbit), and renal failure did not develop. However, if human myohaemoglobin

were injected into these rabbits at the time of release of the limb from compression (or, on occasion, into uninjured rabbits in which the alkali reserve of the blood had been artificially lowered) the complete syndrome, as seen in man, including renal failure, could be reproduced (Bywaters and Stead, 1944). Investigations in the United States confirmed the importance of muscle pigment in association with other factors, such as 'acidaemia' (and an acid urine), in the genesis of the renal failure. The demonstration of similar changes (but without pigment casts) in sulphonamide anuria and acute hydronephrosis has since given some indirect support to the view that the essential action of the muscle pigment is to damage the renal tubules, and to produce, in some way unknown, a sharp rise in intrarenal pressure.

Relating this hypothesis to the clinical problem of treatment, it was considered that giving large amounts of alkaline fluids to the patients as soon as possible after injury might prove successful in preventing renal failure. To this end, a mobile observation team was organised in 1944, with the object of reaching and treating air-raid casualties as rapidly as possible. The number of patients thus treated, however, was insufficient to decide the value of alkali therapy. The wisdom of using alkalis to treat anuria has since been questioned by Maegraith and others (see work on Blackwater Fever described in Chapter 4).

In addition to their pioneer studies of ischaemic muscle necrosis, workers at the British Postgraduate Medical School made a number of clinical and experimental contributions to knowledge of traumatic shock and related problems. Notable among these were investigations of the nature and mechanism of the vaso-vagal fainting reaction after haemorrhage, in which J. McMichael and E. P. Sharpey-Schafer had the co-operation of H. Barcroft and O. G. Edholm from the Medical School, Belfast (Barcroft, Edholm, McMichael and Sharpey-Schafer, 1944; Barcroft and Edholm, 1945–6).

In 1941, some important clinical observations on air-raid casualties were published by R. T. Grant and E. B. Reeve, of the Clinical Research Unit of the Medical Research Council at Guy's Hospital, London (Grant and Reeve, 1941). These workers concluded that the term 'shock', as generally applied to the acute systemic effects of injury, was so ill-defined in meaning that its use without qualification was better avoided. In their view, the only logical approach to the problem of successfully resuscitating the severely wounded lay in making a critical assessment of each case, in order to determine the total reaction of the patient to injury; they emphasised, further, that while blood loss was probably the dominant factor in producing a state of severe illness after trauma, it was not the only one concerned.

The work of the groups at the Postgraduate Medical School and at Guy's Hospital, and of others who observed numerous cases of injury

in 1940–1, thus threw grave doubt upon the value of attacking the 'shock' problem as if wound shock were a single clinical and pathological entity. In consequence, several lines of investigation started for the committee at the beginning of the war were abandoned, the workers transferring their activities to problems likely to be of greater immediate significance to the war effort; among the research schemes terminated as unhopeful were the clinical studies of oxygen therapy for shock.

The various clinical and pathological observations on reactions to trauma had already confirmed that injuries sustained in industrial and other accidents had similar general characteristics to those incurred in air-raids or in battle. Accordingly, since by 1942 the large-scale aerial attacks on London had ceased for the time being, and the accommodation for Grant's Unit at Guy's Hospital had been severely damaged earlier by enemy action, the Medical Research Council made arrangements with the Royal Victoria Infirmary, Newcastle-upon-Tyne, for the Unit to be temporarily transferred there, to study the effects of industrial injuries and of road accidents. Here special attention was given to the respective roles of blood loss, tissue damage and nervous disturbance in producing the clinical pictures seen after severe limb injuries.

In 1942 the War Office and the Medical Research Council, on the recommendation of the Military Personnel Research Committee (Chapter 2), established a Medical Research Section to collect information on the health and well-being of the Middle East Forces. W. C. Wilson of Aberdeen, a member of the Traumatic Shock Committee, was temporarily seconded to the R.A.M.C., with the rank of Lt. Colonel, to take charge of this Section; he had working with him A. L. Chute and E. T. C. Spooner. Among the investigations made by Wilson in North Africa was a detailed clinical study of traumatic 'shock' in 133 men severely wounded in the battle of El Alamein. His reports to the War Office and the Medical Research Council on this work were later published in summary form (Wilson, 1944). He concluded that the most important factor in inducing shock was haemorrhage, and that the early and complete replacement of the lost blood by transfusion, combined with control of bleeding, was the most successful method of treatment.

Towards the end of 1943, it became clear that sufficient clinical material for resuming extensive observations on the relative significance of blood loss, tissue damage and other results of serious injury would be found only on the battlefield. Arrangements were therefore made between the Medical Research Council and the War Office for a special team of workers to study battle casualties in the forward area in Italy. This team, known as 'British Traumatic Shock Team No. 1', was directed by R. T. Grant. It remained in Italy from February 1944

until June 1945, working mainly at C.C.S. level. A full account of the studies of the systemic effects of injury made in the United Kingdom and Italy by Grant and his colleagues during the war has been published in monograph form (Grant and Reeve, 1951); their work supplies what has hitherto been lacking—namely, a detailed clinical description, with illustrative examples, of the varied states of illness that may follow limb and abdominal injuries. The patients studied were followed from soon after wounding until recovery seemed assured or death took place. It was found that the use of certain clinical features, particularly wound size and the level of systolic blood pressure, and the various patterns formed by these features in combination with others, such as pulse rate, face colour and extremity temperature, rendered diagnosis more precise and showed what treatment was required. The principal conclusion from the work was that, both in limb injuries and abdominal injuries due to battle wounds, the circulatory disturbances resulting from blood loss were the chief cause of early death, and early and adequate blood transfusion, continued during and after the primary operation, was the most important factor in saving life—an opinion tallying closely with those of Wilson and many other observers in the field. In cases of limb injury in which the blood volume had been reduced by haemorrhage to 70 per cent. or less of the predicted normal, massive transfusions, sometimes amounting to twelve or more pints of blood, plasma or serum, were often remarkably successful in Grant's experience, and no evidence of over-transfusion was encountered.

After Grant went to Italy, Bywaters was appointed to take charge of the Unit at Newcastle, with the primary object of further investigating the role of tissue damage in the production of shock and allied states. With E. D. Barlow and J. K. Stead, a clinical and biochemical study of 53 cases of accidental injury was made in the Unit; the findings indicated that, in the average severe case of limb injury due to accident, tissue damage was not large compared with that seen in 'crush injury'. In cases of very great severity, however, and particularly in those associated with injury to the main blood vessels to a limb, there was often a considerable amount of muscle necrosis, and some of these patients died in uraemia.

Meanwhile, a direct approach to the problem of a possible 'toxic' factor in shock, resulting from tissue damage, had been made at Sheffield. In 1942, at the suggestion of the Medical Research Council, a small team, consisting of F. W. Holdsworth, H. N. Green and a whole-time assistant, was formed to investigate traumatic 'shock' in industrial accidents. A detailed study of over 100 severely injured patients led to the provisional conclusion that the most important factor in treatment was early surgical extirpation of the damaged tissues. The rapid recovery following amputation of lower limbs with extensive muscle damage induced Green to renew the search for metabolic factors in normal

and injured muscle which might, on release into the circulation, be responsible for some part of the shock syndrome.

This clinical concept was supported by experimental work on ischaemic shock in rats, which also indicated that local fluid loss did not account for the whole sequence of general reactions following injury. Accordingly, many different methods were used in an effort to obtain extracts from muscle that would induce the shock syndrome in animals. As extractions with boiling saline most frequently gave positive results, the possibility that the toxic factor might undergo rapid enzymic breakdown in dying muscle was considered, and, on the basis of earlier work by Dyckerhoff and others, enzyme inactivation was attempted by rapidly immersing normal muscle in acetone. Saline extracts of acetone-ether dried muscle from several species contained a powerful vaso-depressor substance, and induced the gradual development of a shock-like condition when injected by routes other than the intravenous. Bielschowsky and Green fractionated the extracts and showed that the main active substance was adenosine triphosphate ('A.T.P'.). This was one of many derivatives of nucleotide catabolism which were found, on injection into animals, to be capable of producing a state closely resembling that following a prolonged period of hind limb ischaemia (Green, 1943; Bielschowsky and Green, 1943, 1944, 1945). Those of which the biological action was examined in detail caused depression of kidney function, with a pronounced fall in the basal metabolic rate and in liver glycogen, and their lethal effects could be prevented by prophylactic treatment with large amounts of normal saline. It was shown that the magnesium ion strongly potentiated the shock-inducing action of such compounds and also increased the general reaction to a variety of shock-inducing measures (Green and Stoner, 1944); the onset of shock induced either by these compounds or by limb ischaemia could be accelerated by raising the environmental temperature.

Evidence was obtained of the release of such products of nucleotide catabolism from injured tissues. Thus, the adenosine equivalent of rabbit blood was found to rise in shock produced by limb ischaemia, limb trauma, dehydration, burns and other forms of severe tissue damage (Stoner and Green, 1944, 1945); a rise was also noted in man following experimental limb ischaemia. A rise in the nucleotide pentose of the blood plasma was likewise demonstrated after limb ischaemia.

With the object of determining how far these experimental findings had their parallel in cases of wound shock in man, the War Office and the Medical Research Council arranged the formation of a 'British Traumatic Shock Team No. 2', which, under the command of Lt. Colonel Green, made observations on 177 battle casualties in forward areas in N.W. Europe from March 1945 until the end of hostilities (Green, Stoner, Whiteley and Eglin, 1949). With the collaboration of the

Army Blood Transfusion Service, large numbers of specimens of blood and muscle were regularly flown to England for biological and chemical study in Sheffield, while many less specialised tests were done in a mobile laboratory on the spot. To sum up what proved to be a very eventful and laborious investigation, it was shown that, in man, trauma leads to an increase in the blood plasma of substances which can be, and probably are, derived from nucleotide catabolism, a finding in agreement with the animal experiments. Incidentally, in the course of these studies, attention was directed to the problem of fat embolism (see below), and it was later demonstrated experimentally that both in 'A.T.P'. and ischaemic shock the animal becomes more susceptible to the intravenous injection of fat.

It has become increasingly obvious that, if these products of nucleotide catabolism play a part in shock, their action is conditioned by many other factors in severe tissue damage. Haemorrhage, local fluid loss, fat embolism, magnesium, and blood-clotting factors such as thrombin and thromboplastin all greatly increase the susceptibility of the animal to the shock-inducing action of 'A.T.P'. It is evident that, whatever role nucleotide catabolites play in the production of shock, their effects are part of a complex integrated mechanism requiring further study. Meanwhile, an account of many of the relevant investigations by Green and his colleagues has been published in monograph form (Green and Stoner, 1950).

This survey of British research work during the war on traumatic shock and related problems would be incomplete without reference to the studies of the renal circulation published from Oxford University by Trueta, Barclay and others (1946). On the basis of ingenious experiments, these authors put forward the suggestion that the distribution of blood supply within the kidneys is profoundly influenced by central and peripheral nervous stimuli of different kinds, and that the diversion of blood from the renal cortex to the renal medulla resulting from such stimuli, whatever their origin, may produce sufficient cortical ischaemia to account for many forms of traumatic and non-traumatic anuria. Much further research is needed to confirm these observations, but it seems possible that they may have far-reaching implications, not only in disclosing a common pathogenesis for the kidney failure following many different diseases and types of injury, and perhaps in redirecting attention to the long-disputed question of the nervous factor in traumatic shock, but also in suggesting rational new lines of treatment. Responsible experts have expressed their opinion that the chief reason why traumatic anuria was more frequently encountered in the Second World War than in previous conflicts was that greatly improved methods of resuscitation enabled 'shocked' patients who otherwise would have died in the first two days after injury, to survive long enough to develop it. Recent studies on the mechanism of anuria and on the treatment of

uraemia may, if confirmed, provide means of saving such patients from the further and much rarer emergency of acute renal failure, and thus lead to a still higher proportion of permanent recoveries after severe injury.

### FAT EMBOLISM

The occurrence of fat embolism in cases of fracture has been known for many years; that fat embolism could occasionally occur after injuries which involved no fracture was also known before the Second World War. From autopsy studies on a large number of persons killed in accidents or air-raids, Robb-Smith (1941) concluded that pulmonary fat embolism is an almost constant finding in such cases; in many it seemed to have been a major factor in causing death. Subsequently fat embolism of moderate degree was observed in cases of gas gangrene, with and without fracture. This led to an extensive experimental study by A. C. Frazer and his colleagues at Birmingham of the possible aetiological factors in fat embolism (Elkes, 1949).

Pulmonary fat embolism was produced experimentally by fracture, crush injury, injection of *Cl. welchii* toxin and the induction of anaphylactoid reactions. The extent of the fat embolism was much greater when the fat was released from bone-marrow, adipose tissue or muscle than when it was derived from constituents of the blood itself; in the latter event the extent of the lesions was increased by the presence of a concomitant post-absorptive or ether-induced hyperlipaemia. The characteristic signs and symptoms of artificially induced pulmonary fat embolism were attributable to right-sided heart failure and asphyxia. Repeated sublethal intravenous injection of fat was likely to result in cerebral embolism.

The relationship between fat embolism and traumatic shock is still obscure. It is likely, however, that pulmonary fat embolism would be a serious, or even fatal, complication in a patient with incipient peripheral circulatory failure.

### METABOLIC EFFECTS OF INJURY

Complementary to the war-time studies of traumatic shock were investigations into the general disturbance of protein metabolism which results from injury.

*Wounds and Fractures.* In 1939 D. P. Cuthbertson, J. L. McGirr and J. S. M. Robertson, working in the Institute of Physiology, Glasgow, showed that when the femur of the rat was fractured there was a definite loss of nitrogen, sulphur, phosphorus, potassium and, to a less extent, of creatine in the urine, these losses reaching their height about the third day after injury; sodium and preformed creatine remained relatively unaltered. The excess excretion of nitrogen could not be accounted for by loss of muscle substance from the injured limb,

and the authors concluded that a generalised tissue breakdown took place to meet the emergency. This corroborated earlier observations by Cuthbertson on the nitrogen and sulphur losses following certain forms of trauma in man, losses which could only in part be due to disuse atrophy. In 1943, Munro and Cuthbertson found that rats given a protein-free but otherwise qualitatively adequate diet, slightly deficient in energy value, failed to show this characteristic rise in urinary nitrogen after fracture, although animals fed at two different levels of protein intake did so; it was therefore concluded that the excess nitrogen output in the latter was derived from storage-protein and not from essential tissue substance. Munro and Chalmers (1945), continuing this line of work, found that the greater the proportion of protein in the diet of rats before and after injury the greater the amount of nitrogen excreted; the effect of giving a high (25 per cent.) protein diet during the period preceding fracture was immediately lost if the animal was put on a non-protein diet after the fracture.

In 1940, Cuthbertson, working with T. A. Webster and F. G. Young of the National Institute for Medical Research, showed that a crude extract of the anterior pituitary tissue of the ox had nitrogen-retaining and body weight increasing properties when injected into the normal rat. This extract was found to mitigate the characteristic loss of body-weight and the excessive loss of urinary nitrogen and creatine which follow fracture, but it did not appear to increase the rate of healing. In spite of its anabolic potency, anterior pituitary extract had no effect on the total time required for the healing of skin wounds (Cuthbertson, Shaw and Young, 1941). On the other hand, thyroid gland and 2–4–dinitrophenol, which stimulate metabolism, were found to diminish the mean time required for healing circular skin wounds (Barclay, Cuthbertson and Isaacs, 1944).

*Burns.* In the Biochemical Laboratory at Oxford University, Peters and his colleagues found that a rise in urinary nitrogen occurred in rats after burning (Clark, Peters and Rossiter, 1945). Rats burned after feeding on a constant diet containing 10 per cent. casein + 10 per cent. yeast as a source of protein, lost weight and developed a negative nitrogen balance; an increased excretion of urea and creatine in the urine was accompanied by an increased blood urea and a progressive fall in the albumen/globulin ratio of the plasma. Metabolic experiments on rats by Croft and Peters (1945) showed that the nitrogen loss in the urine after burning could be considerably reduced by raising the protein content of the diet from 14 to 22 per cent. on the day of injury. Munro and Chalmers (*loc. cit.*), studying the metabolic effects of fractured femur in rats, as mentioned above, concluded that the greater nitrogen loss observed at the higher (25 per cent.) level of protein intake depended on the rat having gained weight in the period before fracture. Comparison of the nitrogen excretions of injured and control groups of

animals fed initially on a 10 per cent. casein diet on the day of fracture confirmed the results of Croft and Peters; the nitrogen loss after the fracture in these rats was much less than that noted in animals receiving the 25 per cent. casein diet both before and after injury. It may be concluded, therefore, that the extent of the nitrogen loss in the urine following injury depends mainly on the level of protein intake before the injury occurs.

In the experiments of Croft and Peters (1945), nitrogen loss in the urine after injury seemed to be reduced by the addition of 1 per cent. methionine to the diet, although alanine, synthetic amino-acids, and cysteine were without this action. However, Peters and his colleagues repeated the tests in 1945 and 1946, and failed to obtain any effect with methionine upon the nitrogen loss following burning (Gribble, Peters and Wakelin, 1947).

Considerable nitrogen losses in the urine of severely burned patients were reported by A. B. Anderson and E. Semeonoff (1944), working at Glasgow Royal Infirmary in association with the Medical Research Council Burns Unit which was established there in 1942–3. On the other hand, at the Council's Burns Unit at the Birmingham Accident Hospital, J. W. Keyser (1948) found that the average daily nitrogen excretion was excessive in only a few cases of burns, and that in many it was low; he attributed the negative balances to a low intake rather than a high output of nitrogen; patients who ate well were found to be in equilibrium. It is difficult to reconcile this finding with the nitrogen losses after burns which have been reported by other workers, particularly in the United States.

At Oxford E. J. Clark and R. J. Rossiter found a lessened ability of the livers of rabbits to form glycogen from glucose during the first few hours after burning; in the rat, in addition to the rise in blood sugar found in rabbits, a transient rise in blood lactic acid and a fall in muscle glycogen were noted (Clark and Rossiter, 1943). Adrenaline injections produced similar changes. In adrenalectomised rats there was no rise in blood sugar after burning and the carcase glycogen remained normal.

*General Considerations.* The results of the various studies mentioned above led Cuthbertson (1942, 1944, 1945) to conclude that the protein depletion following moderate to severe injury is due essentially to two or more of five main causes: (1) loss of actual tissue; (2) loss of blood or exudate from the damaged area; (3) excessive protein catabolism; (4) infection, if that is superimposed; and (5) disuse or 'reflex' atrophy. He pointed out that the period of reduced metabolism immediately after trauma usually gives way to what seems to be a generalised catabolic phase coupled with local anabolic activity at the zone of healing, and that in injuries such as fractures, dislocations, and even meniscectomies, the protein loss is generally a combined effect of atrophy and

excessive catabolism of body protein. Of these two factors, the excessive catabolism of protein, which in man reaches a maximum usually between the fourth and eighth days after injuries due to direct violence, constitutes the major cause of protein depletion. Following the peak of nitrogen loss there is a gradual decline, though subsequent surgical procedures may cause further disturbance. In burns all five causes generally operate to produce a considerable loss of body nitrogen.

The increased catabolic processes are more general than local; they seem to be conditioned by a mechanism leading either to the raiding of the body protein reserves in order to supply endogenously the necessary substrate of amino-acids or peptide groups for the tissue repair, or to a mobilisation of oxidisable material for the enhanced metabolism of the healing process. The fact that there is a parallel rise in the excretion of nitrogen and sulphur, at least in fracture cases, suggests that there is not a preferential retention of the sulphur-retaining amino-acids. It has been suggested (Cuthbertson, 1942) that the mechanism exists in order to render the healing process independent of food supply, and that the so-called 'toxic destruction of protein' in fever may be explained in this teleological fashion.

Reviewing the practical applications of these studies in war-time, Cuthbertson (1948) concludes that the loss of nitrogen following injury in a previously well nourished patient need not itself give cause for anxiety, provided that steps are taken to replace that which is lost as soon as the acute catabolic period is past; the amount of the nitrogen loss is a measure of the nutritive state of the organism in respect of protein. Where, however, a debilitated patient requires operative treatment, a diet rich in protein should when possible be given before the surgical procedure. This dietary supplement pre-operatively is likely to be more effective than corresponding increments made available in the post-traumatic phase, because a condition of nutritional imbalance is usually present in the latter state.

## Blood Transfusion, Blood Grouping and Blood Products

The organisation of blood transfusion in the Fighting Services, and the establishment and operation of the Emergency Blood Transfusion Services for air-raid casualties in England and Wales, in Scotland and in Northern Ireland, respectively, are described in other volumes of this History. This account is therefore confined for the most part to the research aspects of work on blood transfusion, blood grouping and blood products carried out in the United Kingdom during the war, but the role of the Medical Research Council in planning and maintaining arrangements for the supply of stored blood and of blood products also needs brief mention; it is discussed more fully in the

volume dealing with the Emergency Medical Services for England and Wales, and in the Council's own Report for 1939–45. (See Emergency Medical Services, Volume I, Part II, Chapter 11.)

The activities of the Medical Research Council in this field from about the time of the Munich crisis until the end of hostilities can be summarised under four headings. Firstly, the Council assumed executive responsibility, on behalf of the Ministry of Health, for setting up four depots in the Home Counties for the collection, storage and supply (including transport) of blood for the resuscitation of air-raid casualties in the Greater London area; it was in relation primarily to the work of these depots that the well known M.R.C. blood bottle and transfusion outfit were designed and were purchased in large quantity. The depots were situated at Slough, Luton, Maidstone and Sutton, respectively, and were directed by Dr. Janet Vaughan (Slough), Dr. H. F. Brewer (Luton), Dr. M. Maizels (Maidstone), and successively by Dr. J. O. Oliver, Dr. O. M. Solandt and Dr. J. F. Loutit (Sutton); they not only did magnificent work for the saving of civilian lives during the periods of intensive air attack on London, but were able to give much help to the Fighting Services (especially the Royal Navy and the Royal Air Force, whose own arrangements of a similar kind in the United Kingdom were less extensive than those of the Army); the depots also co-operated effectively with the co-ordinated emergency organisations for blood supply and transfusion which were developed subsequently to cover the needs of the whole country in regard to the treatment both of war casualties and of ordinary medical, surgical and obstetric cases. Secondly and thirdly, the Council, as described below, took the initiative in developing schemes for providing adequate quantities of blood grouping sera and blood products, respectively, as necessary ancillaries to the blood transfusion services; while fourthly, they were concerned throughout the war, as part of their normal function, with promoting research into different aspects of blood transfusion and its related problems. The rapid progress in knowledge of these subjects during the war period was in large measure due to the many investigations carried out—in addition to their routine duties—by the staffs of the London blood supply depots under the Council, and of the Army Blood Transfusion Service directed by Colonel (later Brigadier Sir Lionel) Whitby, the civilian and Army teams working in close co-operation and having their efforts co-ordinated by the Council's Blood Transfusion Research Committee, which included representatives of the Fighting Services and of the Emergency Medical Services. The important research contributions of the Galton Blood Grouping Unit and the Serum Drying Unit, maintained under the Council's direction at Cambridge during the war, will also be discussed in the ensuing pages.

At the beginning of the war it was already appreciated that blood transfusion was likely to play a major role in the resuscitation of the

injured. Experience in 1914–18 had made it clear that the restoration of blood volume was one of the most effective single steps which could be taken to save the life of a seriously wounded man. However, between 1918 and 1939 blood transfusion had been practised on a comparatively modest scale in this country and all needs had been met by obtaining fresh blood from donors as occasions arose. It was evident that the sudden demands which might follow air-raids could be fulfilled only by the establishment of blood banks where substantial reserves of blood could be held in cold storage. Stored blood had been used on a small scale during the latter part of the War of 1914–18 and on a much larger scale in the Spanish Civil War; it had also been used extensively in Russia. In Britain, at the outbreak of hostilities, very few people had any practical experience of the problems of blood storage, and much of the early work at the blood supply depots was devoted to a study of this subject. The work soon involved extensive trials of different preservative solutions. From a practical point of view the most important outcome of these trials was the discovery, in 1943, that acidification of the widely used citrate-glucose solution considerably prolonged the storage life of blood. This advance was soon translated into practice and the acid-citrate-glucose solution became the standard preservative of stored blood, not only for the British fighting and civilian services, but also for the American armed forces. As a by-product of this work on blood storage, much was learned about the physiology of the erythrocyte, and particularly about its survival *in vivo* under different conditions. Information was also gained about ionic exchanges between erythrocytes and plasma, both *in vitro* and *in vivo*.

The limited time for which whole blood could be stored without deterioration led to a demand for a blood derivative or substitute which could be kept for longer periods. To meet this need, liquid plasma and dried serum and plasma were prepared, and new fields for investigation were opened. There was a steady improvement in methods of preparation; at first this was confined to whole plasma and serum for use in resuscitation, but later some fractions of plasma, such as fibrinogen, were prepared for other purposes.

In the field of blood grouping there were striking developments. The American discovery of the Rh factor came at a time when there were specially good facilities for testing large numbers of blood samples, and it soon became evident that blood grouping was a subject of far greater complexity than had previously been realised. The new work on the blood groups which began with the description of the Rh factor has since been shown to have important implications both for practical medicine and for the science of genetics.

Thus it happened that the war provided an environment in which discoveries relating to blood transfusion and its ancillary subjects grew very rapidly, and, while much of the knowledge gained was capable of

immediate application in the treatment of the sick and wounded, a large part of it was of a fundamental nature and of far-reaching significance for medical science in the wider sense. A more detailed account of some of the principal work on blood transfusion, blood grouping and blood products carried out by British investigators during the war years is given below under broad subject headings.

### STORAGE OF WHOLE BLOOD

Initially the blood 'banks' kept at the depots were composed entirely of group 'O' (universal donor) blood collected in a simple sodium citrate solution. The useful life was seven days, and to maintain sufficient stocks of usable blood involved the continual bleeding of donors, and the throwing away of large quantities of blood as it became outdated. An immediate problem was to find methods of lengthening the useful life of whole blood. It was attacked *in vitro* by a study of the physical and chemical changes occurring in the stored blood, and *in vivo* by the study of the survival of the red cells in recipients after transfusion of stored blood. Whitby and his colleagues (1940) and Maizels and colleagues (1940–1) made observations by both these methods. Mollison, Loutit and Young (1942–3) carried the work further. Early results had confirmed that the addition of glucose increased the keeping capacity of stored blood and had shown that this addition allowed refrigerated blood to be kept in good condition for 2–3 weeks instead of one week (Bushby, Kekwick, Marriott and Whitby, 1940; Dubash, Clegg and Vaughan, 1940). Later it was found that slight acidification of the sodium citrate glucose preservative increased the effective storage life to four weeks (Loutit and Mollison, 1943; Loutit, Mollison and Young, 1943–4). Investigations were undertaken (Maizels, 1943–4; Loutit, 1945) in an attempt to elucidate some of the factors involved.

As the war proceeded, the practice of group-to-group transfusion was encouraged, and by this means whole blood from other than universal donors was used. In emergency, however, it was not usually feasible to give individual recipients transfusions of blood of the same group as their own, and group 'O' blood had to be relied upon. This had been the practice formerly in some countries but was not generally considered to be safe. Experimental work confirmed that there were protective factors in the human body which largely neutralised the maleficent action of the antibodies of the group 'O' plasma (Aubert, Boorman and Dodd, 1942). During the whole course of the war remarkably few haemolytic transfusion reactions could be attributed to this cause.

The policy of using universal donor blood almost exclusively for whole blood transfusion, in the circumstances then prevailing, simplified the plans for producing plasma and serum as blood substitutes, since blood of the other groups could be used to provide these

substances. Blood donors of all blood groups thus became of equal value and the burden of blood donation was spread more evenly over the volunteers.

The recognition in 1940 that the useful life of blood could be prolonged made stored blood more freely available, but the idea of using such blood was not readily received by the clinicians, it being held by many that fresh blood was better. An investigation was therefore instituted to assess the relative merits of fresh and stored blood. The four London blood supply depots undertook this work in co-operation (Brewer, Maizels, Oliver and Vaughan, 1940). Their conclusions, rapidly reached, were that in the treatment of acute haemorrhage stored blood was as good as fresh blood, though mild reactions seemed to be more frequent after stored blood transfusion. For non-acute haemorrhage and the supply of red blood cells it seemed obvious that the stored blood would be less effective than fresh blood, but with the improvement effected in the keeping qualities, blood stored for two to three weeks is now known to be but little inferior to fresh blood. The fate of the other formed elements in stored blood was studied by Crosbie and Scarborough (1940); they found that both leucocytes and platelets disintegrated rapidly when stored in sodium citrate. However, since it is generally held that it is not possible to achieve any clinical effects by the transfusion of leucocytes or platelets from one person to another, these results did not alter opinion about the usefulness of stored blood.

### BLOOD GROUPING

The collection and use of whole blood called for precise methods of blood-grouping and for large amounts of high quality grouping sera to carry out the tests. Some months before the war began the Medical Research Council assigned the task of providing serum to the Research Unit in the Serological Aspects of Human Heredity (administered by them on behalf of the Rockefeller Foundation), which had been established under the direction of Professor R. A. Fisher in the Galton Laboratory, University College, London. On the outbreak of war, the Galton Serum Unit, as it was subsequently called, moved to Cambridge. At first undergraduates and residents were able to provide adequate quantities of blood, but as requests for grouping sera increased the net had to be cast more widely. A convenient source proved to be an intake depot of the Royal Air Force, where the medical officers and orderlies co-operated by taking samples of blood, usually about one thousand a week. The group of each blood was determined at Cambridge and the serum further tested for suitability as a grouping reagent. The blood groups were reported and stamped on the identity discs of the airmen. Those whose serum was selected for blood grouping were asked to give blood, and many hundred pints were collected in this

manner. In the end nearly 200,000 airmen had been accurately grouped, the results incidentally yielding very reliable figures for the average blood group distribution in the United Kingdom. For the last two years of the war the Blood Transfusion Services were the main source of supply, and collaboration with a large blood collecting centre proved to be far the most satisfactory method of obtaining grouping serum, permitting large stores to be acquired in a short time.

The publication in the U.S.A. in 1940–1 of the discovery of the Rh blood group factor, and its significance in the aetiology of haemolytic disease of the newborn, was quickly followed up. At the request of the committee, G. L. Taylor and P. L. Mollison wrote joint letters to the medical press, asking to be put in touch with obstetric patients who had been delivered of infants with the disease. The medical profession responded promptly, and in a short time many sera had been tested and the active ones used as reagents in conjunction with animal sera prepared in this country and the U.S.A. Although full information about the importance of the Rh factor did not reach this country till the end of 1941, within a year the American work had been confirmed and additional findings had been recorded (Boorman, Dodd and Mollison, 1942; Taylor, Race, Prior and Ikin, 1942). In the subsequent years remarkable additions to knowledge were made, notably by workers in the Galton Serum Unit (G. L. Taylor, R. R. Race and their colleagues), and a whole series of Rh factors was described and their inter-relationships determined.

Seven 'allelomorphs' of the Rh gene have been isolated, six of which were isolated independently at about the same time in America. An 'incomplete', non-agglutinating, form of anti-Rh has been discovered, which is as dangerous in causing haemolytic disease as is the 'complete' agglutinin. This also was described simultaneously in America. Early in 1944 the collected results were studied by Professor R. A. Fisher, who proposed the theory, which has since received considerable support, that three closely linked loci, each with at least two allelomorphs, were responsible for the Rh groups. The theory demanded one more gene combination and two more antibodies.

The Transfusion Services received invaluable help and advice from the late Dr. G. L. Taylor and his team. Methods suitable for large-scale blood grouping were instituted on lines which could exclude, so far as was humanly possible, either technical or clerical errors. These methods were published (Taylor, Race, Prior and Ikin, 1942), and were subsequently described in more detail in a *War Memorandum* (Medical Research Council, 1943). On the basis of the recommendations, blood grouping of bottles of stored blood can be done very accurately, and it is now extremely rare for incompatible transfusion reactions to be traced to wrong grouping of the donor blood.

### BLOOD GROUP SUBSTANCES

The requirements of the Emergency Blood Transfusion Services and of the Army Blood Transfusion Service for very specific sera containing a high titre of iso-agglutinins for blood group determination, led to a renewal of interest in the chemical nature of the substances responsible for blood group differences. The earlier work of Landsteiner, of Meyer and of Goebel and their colleagues had shown that erythrocytes, gastric mucin, saliva and other secretions contained complex polysaccharides with which were associated blood group specificity. The group A substance, which had been most studied, contained *d*-galactose and N-acetyl glucosamine in equimolecular quantities, together with smaller amounts of at least 15 amino acids and possibly *d*-mannose and *l*-fucose (Morgan and King, 1943). When isolated by gentle chemical methods, purified A-substance dissolved to form extremely viscous solutions which inhibited iso-agglutination of group A cells at high dilutions. Purified A-substance however was not of itself antigenic, but could be combined with the protein component of the somatic O antigen of *Bact. shigae* to form an antigenic complex which gave rise to potent and specific anti-A immune body in the rabbit (Morgan, 1941, 1943). Sera prepared in this manner were used for blood group determination by the Navy.

In seeking for convenient sources of the blood group substances, it was found by Morgan and van Heyningen (1944) that the pseudo-mucinous ovarian cysts which not uncommonly occur as benign tumours in women might contain several grammes of the A-substance, and rather smaller quantities of B- or O-substance. The presence or absence of these substances in cyst fluids was correlated with their presence or absence in saliva and other secretions.

### NATURAL BLOOD SUBSTITUTES

#### LIQUID PLASMA AND SERUM

In December 1939, information was received from the U.S.A. that unfiltered liquid plasma was a useful substitute for whole blood, but serious doubts were expressed as to the advisability of issuing unfiltered plasma, the opalescence of which prevented the detection of contamination by visual inspection. Although much unfiltered plasma was used successfully at the time of the Dunkirk emergency, it was decided thereafter that no product should be issued for transfusion which had not been bacteriologically filtered. Plasma cannot thus be filtered, as clotting occurs in the pads, so attention was directed to serum, which can be readily filtered and gives a clear resultant fluid. The use of serum, however, called for special bleeding, and there was still the plasma from time-expired blood running to waste. Harrison and Picken (1941) tried to solve this latter problem by defibrinating blood as it was taken

from donors, but the method was not generally adopted. Various methods of overcoming the filtration difficulty with plasma were tried; they included recalcification and the addition of serum (Maizels, 1941), altering the *p*H to 10·6 (Bushby and Whitby, 1942), preliminary absorption of the fibrinogen by kaolin (Maizels, 1944). An entirely different approach was made by precipitating the fibrinogen with ether, after which filtration was possible and a crystal clear product was obtained (McFarlane, 1942; Kekwick, Mackay and Record, 1946).

Although the detection of gross contamination in liquid filtered blood products was simple, these had the property, even if sterile, of forming small clots and of developing deposits of a lipo-protein nature, the appearance of which could not be readily distinguished from that of mild contamination. Modifications of the ether process were introduced late in the war, by which all traces of fibrinogen were removed by the addition of human thrombin. By this means a more stable liquid product was obtained. Work on the subject was not complete at the end of hostilities, but the developments had meanwhile been of the greatest importance in supplying the very large amounts of plasma and serum required for the drying plants.

### DRIED PLASMA AND SERUM

While it was impossible to dry whole blood without destroying the red cells, increasing evidence of the value of plasma and serum in resuscitation work gave great impetus to providing these in a dry form. Such products would be stable at all temperatures, capable of being transported to any part of the world without deterioration, and readily reconstituted for transfusion. Though it was realised that the drying of plasma from the frozen state was likely to be the most satisfactory process, it was evident that this would prove very expensive when operated on a large scale. Early in the war, therefore, work was carried out at Manchester on a much cheaper process of spray-drying (Aylward, Mainwaring and Wilkinson, 1940). However, the product proved unsatisfactory, and from then onwards all plans for drying were centred on Cambridge, where, several years before the war, R. I. N. Greaves and his colleagues in the Department of Pathology had worked out a method of condensation drying of proteins. The Medical Research Council had already arranged for investigations to be made there on the preservation by drying of tetanus antitoxin, and these had given such satisfactory results that a drying plant for dealing with large quantities of the antitoxin had been designed. On the outbreak of war the Council proceeded with the erection of drying plants on a similar plan for the drying of blood serum and plasma for transfusion, and, as a consequence, the Cambridge Serum Drying Unit was established under Dr. Greaves's direction. The original plants were able to dry 84 litres of serum per week, the liquid material being provided by the

London blood supply depots, and the filtration of this material being undertaken at a special Filtration Unit started in the Department of Zoology, Cambridge.

From March 1940, to June 1941, the Serum Drying Unit dealt with 18,767 bottles of serum, each containing 200 ml. Most of this dried material went to the three Services, the remainder for the treatment of air-raid casualties and civil cases in the London area. Amongst the other materials dried experimentally were cat, dog, and goat serum and plasma for various workers experimenting on shock in animals. Smaller quantities were dried, during this period, of human blood grouping serum, measles convalescent serum, ether-extracted serum, haemoglobin solutions, pregnant mare serum, foot-and-mouth disease vaccine and therapeutic antisera.

In June 1941, a change was made to drying 400 ml. amounts in the standard M.R.C. transfusion bottle. Preliminary experiments by Lanyon of the Army Blood Transfusion Service had shown that serum could be satisfactorily frozen in the standard bottle by slow rotation in a current of air at −20° C. However, when applied on a large scale, this process yielded irregular results. Greaves then found that very satisfactory pre-freezing could be obtained by spinning the bottles rapidly on their vertical axes at −18° C. Within 18 months over 30,000 bottles of serum were dried in this way for the Royal Navy. In June 1942, work was started on a much larger drying plant as the result of a generous gift to the Medical Research Council from the Wellcome Trustees. This plant came into operation on February 1, 1943, and between that date and September 1945, when it was closed down, it had dried close on a half million bottles of plasma and serum. The output of this large plant supplied within that time the total requirements of the Royal Navy and the civilian population, a proportion of the Army needs, and the home needs of the R.A.F.

During the early war period, technical advice and assistance were given by the Serum Drying Unit in the design of drying plants for the Wellcome Physiological Research Laboratories, the Army Transfusion Service and the Scottish Transfusion Service; in the later war period, advice was chiefly sought for the design of drying plants for penicillin production. A full account of the equipment and work of the Unit has been published by Greaves (1946).

## COMPARISONS OF THE VALUES OF WHOLE BLOOD, SERUM AND PLASMA IN TREATMENT

Early studies suggested that plasma transfusions were as effective as transfusions of whole blood in restoring the blood volume after haemorrhage, and that in the treatment of wound shock, plasma could largely replace blood (Buttle, Kekwick and Schweitzer, 1940; Grant and Reeve, 1941). Later, however, it came to be widely accepted that haemorrhage

was the chief cause of wound shock and that transfusion of whole blood was the most effective means of restoring the patient; and furthermore, that it was most important to maintain the amount of circulating haemoglobin above a certain level (Grant, 1942). Still later, the realisation that transfusions of pooled plasma carried a much greater risk of inducing an attack of hepatitis than did transfusions of whole blood, led to an even greater swing of opinion in favour of blood. Serum was found to be substantially as effective as plasma in the treatment of oligaemic shock, although no precise comparisons were attempted.

### STERILITY OF WHOLE BLOOD AND OF BLOOD PRODUCTS

The maintenance of the sterility of blood and blood products is a source of anxiety to a transfusion service, and much work was undertaken on this problem. A series of tests was made to ascertain the incidence of infection when using the bleeding technique adopted. It was found that in some 2 per cent. of donations the blood obtained showed bacterial contamination as it entered the bottle, probably from bacteria lying in the deeper layers of the donor's skin, though in how many of these instances the blood might have become sterile later by the action of antibacterial substances present in it was not determined. Any method of sampling the actual bottles of blood for bacterial contamination was held to be undesirable. It was therefore decided that no routine tests could be made for the sterility of blood, but that rigid adherence to an aseptic bleeding procedure, and the bleeding of donors by teams specially trained, were the best means of minimising the risk of bacterial infection. These procedures proved very satisfactory in large-scale practice, although one or two deaths following transfusion could be attributed to the giving of infected blood (see below).

The preparation of large quantities of blood products, which are in themselves excellent culture media for bacteria, raised technical difficulties of considerable magnitude. The margin of safety would have been increased if a suitable antiseptic could have been added. Antiseptics such as 'Merthiolate', phenyl mercuric nitrate, the sulphonamides, acriflavine, etc., were accordingly investigated from this point of view (Mackay, 1941). All failed to satisfy the exacting requirements, either because the introduction of large quantities of antiseptics in massive transfusions was clinically undesirable, because they failed to kill all the possible contaminating bacteria, or because their action did not persist over the long periods of time during which the liquid products were stored. Efforts had therefore to be directed towards the development of techniques to avoid bacterial contamination. The regular testing of the product at various stages in its preparation, and the precaution of keeping the fluid product in its final container for seven days in the incubator at 37° C. and for fourteen days at room temperature before issue, which was adopted as a routine procedure,

ensured that no product was released which had been infected at any stage in its preparation. When the material was to be dried, it was insisted that this should be carried out in the final container, so as to minimise the risk of infection.

### EFFECTS OF BLEEDING UPON THE DONOR

It was to be expected that when volunteers were venesected by the thousand some ill effects would be reported. Poles and Boycott (1942) observed spontaneous fainting, or fainting provoked by sitting or standing, in 2·8 per cent. of the first 10,000 donors bled by the Army Transfusion Service. One important finding was the increase in fainting brought about by withdrawing 540 ml. rather than 440 ml. of blood from donors. Later, a more widespread survey was made at the civilian transfusion centres to determine both the immediate and late effects of blood donation (Medical Research Council, 1944). It was concluded that, apart from the advisability of excluding donors who gave a history of fainting either associated or unassociated with blood donation, no factor open to correction was involved. Delayed fainting or faintness occurred in 1·2 per cent. of men and 1·8 per cent. of women donors. As against 14 per cent. of donors who experienced some discomfort, however small, 10 per cent. felt especially fit after giving blood.

### COMPLICATIONS OF TRANSFUSION IN THE RECIPIENT

The Blood Transfusion Research Committee watched with some anxiety for accidents or deaths in recipients following transfusion, a not unlikely event when large numbers of badly injured patients were being given massive transfusions under emergency conditions. An effort was made early in 1940 to collect reports of any such accidents or deaths occurring in the London area. The analysis of the small number of reports received indicated that very few of the accidents and none of the deaths reported could be attributed to the transfusion. On the other hand, two instances of death following transfusion came to the notice of the committee from other sources. In both cases it was associated with the giving of blood containing a diphtheroid organism which grew at temperatures as low as $+2^{\circ}$ C., and might have been due to inadequate sterilisation of the transfusion equipment. These events led the Committee to stress the paramount importance of ensuring the proper working of the autoclaves in use; a special article on the subject was published from the Slough Blood Depot (Spooner and Turnbull, 1942).

Apart from the rare accidents following transfusion, it was common to observe reactions characterised by evanescent rigors and rise of temperature after the giving of blood, plasma or serum. This problem was constantly before the committee. Every effort was made to eliminate such reactions by the careful preparation of all equipment and

transfusion material: yet, though their incidence fell, they still occurred. Many attempts, both clinical and experimental, were made to elucidate the nature of these reactions, and the committee finally decided that the only hopeful approach was to prepare special batches of material from the pooled serum or plasma of a very large number of donors, and to issue these in bottles all containing identical material, to special investigators working to exactly the same standards. This plan was nearly in operation when serious doubt arose as to the advisability of using material prepared from a large number of donors, owing to the risk of homologous serum jaundice (see below). At about the same time, the war ended, there was a rapid redistribution of hospital staffs, and the investigation was abandoned.

### TRANSMISSION OF DISEASE BY TRANSFUSION

The ill effects discussed above were those following closely upon transfusion, but the possibility of disease being conveyed to the recipient and developing after an interval had also to be considered. In 1937 an event had occurred in which several deaths due to acute hepatic necrosis followed the giving of adult human serum for the prophylaxis of measles. The committee had, therefore, in mind from the very beginning that the use of human serum and plasma for transfusion might occasionally be followed by jaundice or acute hepatic necrosis.

The committee repeatedly brought the possible risk of post-transfusion jaundice before those responsible for transfusion; but it was not until 1942 that clear evidence of the occurrence of post-transfusion jaundice was obtained, when out of a series of patients who had received serum for transfusion several developed jaundice some fifty to sixty days later. About the same time additional evidence of its occurrence was obtained in a series of cases transfused with bottles of serum from the same batch. In those days it was the custom, in order to decrease the losses due to filtration, to pool the serum and plasma from the blood of 500 to 1,000 donors, and it was thus possible for a single donor to infect a large number of bottles.

Although workers with much experience of transfusion felt that jaundice as a complication must be rare, a follow-up of cases transfused with plasma or serum was instituted. In the selected area, it was found that jaundice occurred in 7 to 10 per cent. of those transfused with filtered serum or plasma. The reason why it had been missed was that the disease was in the vast majority of cases very mild, and no deaths had occurred. In another area almost identical results were obtained. On the other hand, in a follow-up of 1,000 cases receiving only whole blood (3,800 bottles) the incidence was less than 1 per cent., suggesting that the donors responsible must be relatively uncommon. This was supported by work in which samples of fresh serum from ten different donors were injected into a similar number of recipients without

jaundice occurring. Analysis by the Ministry of Health of the records of Service patients treated in E.M.S. hospitals for wounds and other conditions showed, nevertheless, that the incidence of jaundice was much higher in those who had received transfusion than in those who had not, and that the small number of fatal cases of jaundice among the patients all occurred in the former group. In interpreting these results, it had to be remembered that in addition to receiving transfusion, many wounded men were given other remedies by injection, and the risk of the transmission of jaundice by this means was not negligible.

Administrative action on two lines was taken, namely to reduce the number of donors contributing to a plasma or serum pool to ten as a maximum, and to emphasise that plasma or serum should be used only in cases in which, owing to urgency, whole blood could not be used. Follow-up investigations have since been undertaken upon the incidence of jaundice in cases receiving plasma or serum from these small pools. In one such investigation, Lehane *et al.* (1949), found that the incidence of homologous serum jaundice was not significantly greater following the transfusion of small-pool plasma than following the transfusion of whole blood (1·3 per cent. as against 0·8 per cent.). Apart from jaundice there was no instance of the transmission of any disease by transfusion.

The problem of homologous serum jaundice is discussed further in Chapter 4.

### BY-PRODUCTS OF THE TRANSFUSION SERVICES

*Fibrinogen, Thrombin and Fibrin Foam.* The preparation of fibrinogen, thrombin and fibrin foam from human plasma by Cohn and his colleagues in the United States made available haemostatic materials which were of much practical value in neurosurgery. A supply of these products was generously provided by the American authorities for trial by British Service and civilian surgeons. The Blood Transfusion Research Committee considered the possibility of having similar blood derivatives prepared in Britain, but it was clear that it would not be practicable to obtain the elaborate equipment necessary for the Cohn process during the war. The importance of such materials was, however, brought to the attention of research workers, with the result that early in 1944 the ether precipitation method mentioned earlier in this chapter was successfully modified so that these materials could be obtained by means of simple laboratory apparatus, with yields so high that the process could easily be adapted to production on a larger scale. This was undertaken at the Lister Institute, London, and in 1945 the substances were issued to surgeons. The supply has been continued, and surgeons are now unwilling to undertake certain operations unless these materials are at hand.

*Serum and Globulin for Use against Measles.* Under the abnormal conditions of war-time the possibility of widespread epidemics of measles

in children gave rise to special anxiety. The Blood Transfusion Research Committee was therefore invited to help with the preparation of large quantities of adult human serum for the prophylaxis of this disease. The committee had already successfully investigated the possibility of preparing filtered serum in large quantities, and the only difficulty that remained was to obtain the blood. It was decided to issue an appeal for donors, and to emphasise that donors of other than the universal donor group could be used. The appeal met with complete success, and in February 1940, the committee was able to report that some 6,000 doses of the serum were available.

In addition to adult serum for the prophylaxis of measles, the committee had in mind the use for the purpose of the immune globulin which was being prepared by Dr. Cohn in the U.S.A., and had been tried successfully here on a small scale. In 1945 the ether precipitation method (see above) was further modified and the preparation of immune globulin undertaken. The pilot experiments indicated that the method would prove effective, but owing to the pressure of work more essential to the war effort its development was postponed till after the end of hostilities. It has since been brought to fruition.

### ARTIFICIAL BLOOD SUBSTITUTES

Throughout the war, the Blood Transfusion Research Committee had constantly in view the improvement and standardisation of transfusion methods and equipment. Attention was also given to the potentialities and limitations of artificial blood substitutes such as pectin, isinglass, and periston (a product of German origin). It was concluded, however, that none of the artificial blood substitutes available in this country during the war competed in practical value with plasma and serum.

## Publications relating to Chapter 3

The publications listed below are arranged under the headings of the corresponding sections and sub-sections of this chapter, but the lists include many papers dealing with studies by British investigators which have not been specifically mentioned in the text. Where a publication has been mentioned in more than one sub-section it is listed under each heading for convenience of reference.

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# CHAPTER 4

# WAR DISEASES

In this category are included a number of diseases which caused, or threatened to cause, so serious a drain on man-power in particular theatres of war as to demand intensive research on methods for their control. Where an infectious or other disease showed signs of becoming a major health hazard to the troops or the civilian population under war conditions, it was usual for the War Office or the Ministry of Health to invite the aid of the Medical Research Council in dealing with it; the planning of investigations on a suitable scale was generally entrusted by the Council to expert committees, appointed specially for the purpose, which included representatives of the Fighting Services, and of the Government departments mainly concerned; examples of such *ad hoc* committees were the Committee on Tuberculosis in War-time, the Malaria Committee, the Typhus Committee and the Jaundice Committee (see Appendix I). On some of the more important health risks of war-time—such as tuberculosis, malaria and influenza—the Medical Research Council had already promoted extensive research programmes before the war; on others, special schemes of research were initiated during the war period to meet emergency situations—for instance, the greatly increased prevalence of infective hepatitis under war conditions. In the study of many disease problems—for example, those relating to the prevention and treatment of malaria and the typhus fevers, which involved the testing of numerous synthetic drugs, insecticides and insect repellents—the British war-time research programme was closely integrated with the activities of workers in other Commonwealth countries and in the U.S.A.

Certain omissions from this chapter call for explanation. That no specific mention is made here of work on such important causes of wasted man-power as the venereal diseases and the commoner skin infections is due to the fact that most of the war-time research on these diseases consisted of clinical trials of the sulphonamides and, later, penicillin in their treatment (see Chapter 7). Accounts of the general advances in knowledge of these and many other conditions, achieved during the war, are given in the volume of the Medical History dealing with Medicine and Pathology; there, too, will be found descriptions of the various inquiries organised by specialist medical officers in the Forces and the civilian Emergency Medical Services into the nature and treatment of the psychological effects of battle experience and of air-raids.

Among the diseases which first came into prominence during the war years was the group of non-bacterial respiratory infections known as primary atypical pneumonias. Much work on the nature of these conditions was carried out by Service and civilian medical officers, as described elsewhere in the History. Since, however, it was not deemed necessary to divert scientific man-power to an intensive study of these infections in the United Kingdom, in duplication of the work on the subject which was already being undertaken on a large scale in the United States, they do not receive further mention here. On the other hand, a brief note is included on the rickettsial disease Q fever, originally described in Australia, which was recognised endemically in Greece early in the war and assumed epidemic proportions during the Italian campaign of 1944.

The short account of war-time studies of poliomyelitis in Colonial territories which closes the chapter is of interest in relation to the epidemiological problems raised by the greatly increased incidence of this disease in the United Kingdom in recent years.

## Dyspepsia in the Army, 1939–40

Early in the war it became apparent that indigestion was the largest medical problem among the sick invalided back to the United Kingdom from the B.E.F. in France. There was much uncertainty as to what this disorder represented and how it had come about. At the suggestion of Colonel H. L. Tidy (now Sir Henry Tidy), the Royal College of Physicians of London decided to use the Leverhulme Trust Fund to promote an investigation. Dr. Charles Newman and Mr. Reginald T. Payne were appointed to carry out the work, and they examined 287 Service patients under treatment for indigestion at various hospitals (Payne and Newman, 1940); advice on the statistical aspect of the inquiry was given by the late Professor M. Greenwood. Eighty-nine per cent. of the subjects examined were found to have gross organic disease, usually duodenal ulceration; 92 per cent. of the ulcers had apparently been present before the war, and had relapsed, not originated, in the Services. The patients with old ulcers had been able to carry on satisfactorily with civilian diet, but had broken down on Army food, which inevitably was unsuitable for ulcer patients. Malingering was extremely rare at that stage of the war, but there was a certain number of neurotic cases; in these dyspepsia seemed to have replaced the effort syndrome which was so common in the War of 1914–18.

This investigation was among the first of an extensive series of studies of the incidence and significance of gastro-duodenal disorders in the Fighting Services and the civilian population, which were carried out by many different workers at successive stages of the war. Accounts of most of the inquiries were published in the medical press, and the problem of the dyspepsias in war-time is fully discussed in the Medicine

and Pathology volume of the Official Medical History. The various studies which followed this organised pilot survey are not, therefore, reviewed here.

## Tuberculosis

In the first two years of the war there was evidence of a significant increase in the mortality from tuberculosis in the United Kingdom, reversing the favourable pre-war trend of the death-rate from this disease. Accordingly, in the autumn of 1941, the Ministry of Health requested the Medical Research Council to appoint a Committee on Tuberculosis in War-time to examine the extent and causes of this increase, and to advise on possible preventive measures; the membership of the committee, whose Chairman was the late Viscount Dawson of Penn, is given in Appendix I.

The committee's report (Medical Research Council, 1942) showed that, up to the time of its survey (the early months of 1942), all age-groups had been involved to some extent in the increased mortality, and that the increase was common to both pulmonary and non-pulmonary forms of tuberculosis. The report emphasised the importance of the social background of the disease, and the probable bearing on its rising death-rate of the very complex, and in some respects radical, alterations in the national way of life between 1939 and 1941. Some of these changes increased the risks of infection and others decreased the resisting power of the individual. Among such factors were the black-out; overcrowding in many homes due to the destruction of others by bombing; movements of population due to evacuation; the recruitment to industry of large numbers of persons not previously engaged in factory work; diminished resistance due to fatigue from long hours of duty and difficult travelling conditions; and in certain categories of persons, a possible inadequacy of rations. The report made a number of practical recommendations for dealing with the problem, including the application to the civilian population of the technique of mass miniature radiography (fluorography) of the chest, which had already been adopted by the Royal Navy (see below), as a means of detecting unsuspected dangerous sources of infection on the one hand and early cases of pulmonary tuberculosis in need of care and treatment on the other. The committee also recommended various measures of a public health and administrative nature which had the aims of encouraging the tuberculous patient to seek early advice, of easing the economic position of himself and his family while he was under treatment, and of assisting him in rehabilitation and return to suitable employment. Some of the main recommendations—notably the introduction of a national scheme for civilian mass radiography, and of a scheme for family allowances for the tuberculous—were rapidly implemented by the Health Departments, and their adoption may well have helped to maintain the fall in

the death-rate from tuberculosis which occurred in the second half of the war. They should also assist in the long-term attack on this disease.

### MASS RADIOGRAPHY OF CIVILIANS

Before routine mass radiography could be introduced by local authorities throughout the country, it was necessary that a standardised instrument of high quality should be available. The transportable sets ultimately sponsored by the Ministry of Health and the Department of Health for Scotland embodied the essential recommendations on design made by a technical sub-committee of the Medical Research Council committee referred to above. The first set to be produced was used for a pilot survey on selected civilian groups by a special unit of the Medical Research Council, whose members were Miss Kathleen C. Clark (of the staff of Ilford, Limited), Dr. P. D'Arcy Hart (the Secretary of the Council's committee), Dr. Peter Kerley and Dr. B. C. Thompson. The objects of the investigation were to establish standard technical and administrative methods so as to assist those subsequently responsible for the national scheme; to estimate the incidence of tuberculosis during war-time in various civilian groups, and thus to assess the demands likely to be made on the tuberculosis services as a result of mass radiography; and to throw further light on the epidemiology of the disease. The survey took place during 1943, and it covered approximately 23,000 persons from two factories, a large office group and a mental hospital, all of which were in Greater London. The report of this work (Clark, Hart, Kerley and Thompson, 1945) proved a valuable guide to the administration and technique of civilian mass radiography in its wider applications in industry and elsewhere, as well as containing the statistical results of the unit's own survey. The incidence of persons with significant tuberculous lesions newly revealed by mass radiography in London-employed groups appeared to be 1·0–1·5 per cent.; 0·3–0·4 per cent. were in need of immediate treatment and the rest required observation while continuing work. The incidence in mental hospital patients was about three times as high as in the employed population.

### THE PROPHIT SURVEY

An important event during the war was the completion and analysis of the ten-year inquiry (1935-44), carried out under the Prophit Tuberculosis Research Trust of the Royal College of Physicians of London, into the circumstances of the development of tuberculosis in young adults—particularly young nurses coming into a sphere of exceptional exposure to infection, namely the hospital environment. The population followed up consisted mainly of over 5,000 student nurses entering various large London general hospitals; although other groups (e.g. medical students, home-contacts) were originally included,

making another 5,000 subjects altogether, the war interfered with the continued examination of these, so that the findings in regard to them could be analysed in only a limited way. In the subjects observed for sufficient periods the early natural history of such tuberculous lesions as occurred was studied in relation to initial skin tuberculin-sensitivity (as revealed by the Mantoux test) and to subsequent changes in this sensitivity; to geographical, " racial " and other possible aetiological factors (the morbidity was significantly higher among the nurses of Irish and Welsh origin than among the others); and to the degree of duration of exposure to infection while in the scheme. Among the conclusions were the following: the greater the degree of contact with infection, the more likely was the disease to occur; it occurred more often in subjects originally tuberculin-negative who became tuberculin-positive than in those who reacted to the Mantoux test on entry, though the latter were far from being exempt; genetic immunity was important since, other things being equal, different ethnic groups differed in their incidence of tuberculosis. Various practical recommendations for the improved protection of young adults, especially hospital workers, were made in the report on the results of the Survey (Daniels, Ridehalgh, Springett and Hall, 1948). They included periodic tuberculin-testing and X-raying to discover the early lesion; reduction of unnecessary sources of heavy exposure to tuberculous infection, e.g. in the hospital environment; a close watch on adequacy of diet and on hours of work and living conditions; and consideration of vaccination with B.C.G. of the initially tuberculin-negative among young adults (e.g. nurses and medical students) about to enter an environment involving repeated exposure to infection. A number of the recommendations, including that relating to B.C.G. immunisation of young persons likely to be exposed to special risk, have since been implemented.

### THE DISTRIBUTION AND AETIOLOGY OF NON-PULMONARY TUBERCULOSIS IN GREAT BRITAIN

The finding by the Committee on Tuberculosis in War-time that the increase in non-pulmonary tuberculosis during the first two years of the recent war had affected persons at all ages, and not merely children as in the First World War, made it important to determine whether this increase was due mainly to infection with the human or the bovine type of tubercle bacillus. A conference was summoned by the Medical Research Council in January 1943, to plan a nation-wide survey on these lines. In England the inquiry was directed by Professor G. S. Wilson and Dr. D'Arcy Hart and was carried out by the Emergency Public Health Laboratory Service in co-operation with numerous hospital laboratories; in Wales it was directed by Professor W. H. Tytler and Dr. V. D. Allison; and in Scotland by a committee with Professor J. W. S. Blacklock as convener.

In England material provided by hospital pathologists in different parts of the country was examined at twenty-five typing centres. In addition, information was obtained on factors such as the age, sex and occupation of the patient, on recent change of residence, on the milk supply, and on contact with open cases of tuberculosis, which might have had a bearing on the genesis of the disease. The information obtained in this way showed that, with the possible exception of bone and joint disease, the bovine type of tubercle bacillus was apparently responsible for much the same proportion of non-pulmonary tuberculosis as before the war; that infection with the bovine type was much more frequent in some parts of the country than in others, particularly in the North-midland and North-western areas; that, apart from the first five years of life, when the incidence was the same in both sexes, the proportion of bovine to human infections increased progressively in females with age till, in the group 15 years and over, it was approximately double that in males; that, in contrast with previous experience, the maximum incidence of infection with the bovine type of bacillus was now in the 5–9 instead of the 0–4 age group, suggesting that greater care in infant feeding had resulted in the partial protection of the pre-school child, but that the introduction of the milk-in-schools scheme, without adequate measures to safeguard the purity of the milk, might have contributed to the increase in the proportion of bovine infections in older children; and that the raw milk supply of the country was almost as heavily contaminated with tubercle bacilli as it had been twenty years before. The value of this information for supporting the introduction of compulsory pasteurization of all but T.T. milk was self-evident.

In Wales the proportion of human infections caused by the bovine type of bacillus was considerably lower than in England—17 per cent. in contrast to 26·3 per cent. The probable reasons for this were that a much higher proportion of the dairy herds in Wales were 'attested' and that a considerable proportion of the milk in the larger towns of South Wales was pasteurized or heat-treated; both these factors would tend to lessen the risk of milk-borne tuberculosis.

Taking the figures for England and Wales together, it was estimated that about 24 per cent. of all cases of non-pulmonary tuberculosis were due to infection with the bovine type of tubercle bacillus, and that between 1,300 and 1,400 persons died in 1944 from non-pulmonary tuberculosis of bovine origin.

In Scotland a study of the type of tubercle bacillus causing meningeal or surgical tuberculosis was made by a team of workers during the war years 1943–44. The Scottish investigation, due to differences in geography and the distribution of population, did not follow quite the same lines as those in England and in Wales. For the purposes of the study Scotland was divided into five regions, viz: (1) the Northern, with

a collecting centre at the Royal Northern Infirmary, Inverness, under the control of Dr. H. J. R. Kirkpatrick, (2) the North-eastern, with a centre at Aberdeen, under Dr. John Smith, the City Bacteriologist, (3) the Eastern, with a centre at Glenlomond Sanatorium, under the late Dr. W. T. Munro, (4) the South-eastern, with two centres at Edinburgh, under Dr. Agnes Macgregor and Professor T. J. Mackie, and (5) the Western, with two centres at Glasgow under Dr. K. J. Guthrie and Professor J. W. S. Blacklock respectively. The laboratory at the Glasgow Royal Infirmary, under Professor Blacklock, acted as the main typing and advisory centre for the whole of Scotland, and thus uniformity as regards typing and methods was assured.

A form requesting details of the clinical and family history, occupation, housing conditions, contact with cases of tuberculosis, the nature of the milk consumed and any recent change of habitation was sent to all practitioners or hospitals sending specimens, in addition to the Medical Officer of Health or Tuberculosis Officer of the area in which the case occurred. The information gained showed that bovine infection was more frequent in surgical than in meningeal tuberculosis, and that different percentages of bovine infections occurred in these conditions in various regions. The bovine percentage was higher in those regions, composed mostly of rural areas, where more raw milk was consumed than in the more highly industrial regions, where heat treatment of milk was extensively practised. In the case of meningeal tuberculosis, the highest percentage of bovine infection occurred in the 0–5 years group, though in surgical tuberculosis such infection was commoner in the 5–10 years group than at any other period. The total bovine percentage was practically the same for both sexes in meningeal tuberculosis, but in surgical tuberculosis the percentage of bovine infection was slightly higher in females.

Compared with the results obtained by previous investigators, the percentage of bovine infection in meningeal tuberculosis in the present investigation was lower by approximately one-half and in surgical tuberculosis by one-third, the greatest reduction being in those areas where compulsory heat treatment of milk had been instituted.

It was estimated from the results of the investigation during 1943-44, that 115 of the 1,033 deaths from meningeal tuberculosis were due to infection with the bovine bacillus, and that of the 20,433 notified cases of surgical tuberculosis, 6,906 were caused by this type of bacillus.

### PULMONARY TUBERCULOSIS IN THE FIGHTING SERVICES

Research within the Services on pulmonary tuberculosis was both stimulated and dominated by the Royal Navy's adoption of fluorography (mass miniature radiography) for its detection in 1939. The method had not been used previously in Great Britain, nor had there

been any really large-scale radiological surveys of the incidence of the disease among the apparently healthy. Fluorography had been developed to a high stage of efficiency by D'Abreu in Brazil, who published his work on the subject in 1936. Permitting rapid and relatively inexpensive photography of the fluorescent screen image of the chest, it was ideally suited to Service requirements, and its successful application by the Royal Navy was followed by its adoption in 1941 by the Royal Air Force and later, in a modified way with mobile units, by the Army. In the Dominions, too, fluorography or direct radiography was used extensively to exclude cases of tuberculosis from the Armed Forces and to diagnose cases within them. Thus, in Canada, after the second month of the war, a radiological examination of the chest was made compulsory for all recruits; while both direct radiography and fluorography were employed extensively in Australia, New Zealand and South Africa for the same purpose.

The earlier published reports in this country (Dudley, 1941; Fitzpatrick, 1941; Trail, 1942; Gilchrist, Graham and Davies, 1942; Warner, 1942; Brooks, 1943; Webster, 1943) were concerned either with the incidence and types of pulmonary tuberculosis revealed by fluorography among the apparently healthy, or with details of technique and procedure which experience had shown were well suited to Service routine. For the individual, the advantages of early diagnosis were stressed. Here as elsewhere in the world, the incidence of pulmonary tuberculosis revealed in males was found to rise with the age of the individuals examined; in women, however, the greatest incidence tended to occur between the ages of twenty and thirty. The methods of investigation of cases thus disclosed, and the criteria for the diagnosis of active pulmonary tuberculosis, varied very considerably in different Services, so that the recorded results were not, in these respects, strictly comparable. In the Royal Navy and the Royal Air Force, fluorography was used to separate those whose chests were abnormal from the remainder. Full-scale radiological examination of the abnormal individuals then followed, and those found at this stage to have significant abnormalities were investigated in hospital.

The most difficult and pressing problem following the use of fluorography was that of the proper disposal of those found to have apparently inactive pulmonary tuberculosis, for the fate of such cases was unknown and they were numerically an important group. Those shown, at hospital investigation, to have active disease needed and received therapy by the accepted and available methods; those with arrested disease were returned to duty. The shortage of man-power, and more especially of trained men, however, made it essential to avoid unnecessary wastage. An extensive investigation of this problem was undertaken in the Royal Navy, where men with apparently inactive minimal pulmonary tuberculosis were observed and repeatedly examined while on selected

home shore service. The results of a two-year study of approximately 2,000 cases were published by Brooks (1944), who showed that the younger the individual with this type of lesion, the more likely was relapse to become evident under the conditions of observation; while, irrespective of age, the longer a lesion remained stable the less likely was relapse subsequently to occur. In the same investigation the most sensitive method of assessing activity of pulmonary tuberculosis was found to be alteration in the appearance of a lesion shown by repeated radiological examination over a period of time. Webster (1943) had emphasised that the discovery of tubercle bacilli remained the most satisfactory proof of the activity of tuberculous lesions. A valuable analysis of the symptoms in some 650 cases revealed by fluorography in the Royal Air Force was published by Trenchard (1943): in the difficult problem of assessing the activity in these cases it remains of help.

Sir Sheldon Dudley, to whom the introduction of fluorography in the Royal Navy was largely due, had examined the potentialities of this and similar methods for the control of pulmonary tuberculosis from an epidemiological point of view. He had pointed out that if tuberculosis in adult life were preponderantly the ultimate result of infection in childhood, repeated fluorography could do nothing to reduce its incidence in the Service; but that, if not, the method should be of value in reducing the number of unsuspected infectious cases below the unknown critical level needed to ensure the perpetuation of the disease. Evidence from many sources demonstrated that primary infection commonly occurred in adolescence and adult life. Studies by Brooks (1942, 1944, 1946) and Trail (1942) made it seem probable that a not inconsiderable proportion of the cases revealed by fluorography were either examples of primary tuberculosis or were cases in which progression to 'adult type' disease had continuously occurred following recent primary infection. To this extent the first hypothesis was refuted; and, in addition, abundant evidence was forthcoming within the Royal Navy that adult type pulmonary tuberculosis almost certainly developed by re-infection due to continued close contact with infectious cases. Thus, localised epidemics of the disease were occasionally reported in ships which had been at sea for long periods, many of the cases showing radiological evidence of the calcified residua of past infection.

The fluorographic apparatus and personnel available in the Royal Navy were never, during the war, sufficient for their purpose. None the less, during this time repeated annual fluorography, which was attempted for the whole force, as well as the examination of recruits on entry, yielded much valuable information about the epidemiology of pulmonary tuberculosis. Thus, repeated fluorography revealed an incidence of 2·4 new cases per thousand at an interval of one year,

3·5 per thousand at an interval of two years, and 7·3 per thousand at an interval of three years between examinations. It also showed that these new cases increased in incidence with age just as did the cases found at first examination, which had in the aggregate amounted to 12·7 per thousand of the entire force. Furthermore, a year by year examination of the incidence of tuberculosis in recruits showed a rise at all ages which reached a peak in 1943, and was followed by a fall which persisted till 1945, having by then reached levels just below those of 1939. It was not easy to correlate these findings with dietetic deficiency or with the strain of war. A more likely explanation was an increased hazard of infection due to the emptying of the sanatoria in 1939–40, followed by the intensification of aerial bombardment in 1940–41, favouring contact between the infectious and other classes of the community—a hazard which was correspondingly lessened when the sanatoria once more reverted to their normal usage and when the main fury of the aerial attack abated.

Adamson, Warner, Keevil and Beamish adduced further evidence of the significance of infection of adults from a study of the incidence of pulmonary tuberculosis and pleurisy with effusion in the Canadian Army, whose men had been subjected to X-ray examination at enlistment. In the time covered by their investigation (1939–44) about half the Army had been in Canada and half in England, where a much higher risk of infection by tubercle bacilli was known to prevail. The incidence in 1944 of pulmonary tuberculosis was 58 per 100,000 in the Army in Canada, and 370 per 100,000 in the Army in England. Pleurisy with effusion in the Army in Canada showed the same incidence as obtained among the civilian population, while in the Canadian Army in England the incidence was nearly four times as high.

From the Royal Air Force, Conybeare (1946), in a study of the incidence of pulmonary tuberculosis (symptomatic) following pleurisy with effusion, found a morbidity of 14·5 per cent. some three and a half to six years after the latter disease. Brooks (1946) in a series of Royal Naval patients with pleurisy with effusion, observed on home shore service over a period of one to three years, reported an incidence of symptomatic pulmonary tuberculosis of 11 per cent., while a further 21 per cent. developed fluorographic evidence of the disease.

MacLean (1948), from an extensive investigation of Royal Naval patients who had had pleurisy with effusion, computed the probable morbidity at 25 per cent. in a five year period. In attempting to assess the likelihood of subsequent phthisis he concluded that long duration and great size of the effusion, and its occurrence in the third decade of life were all significant. On the other hand, a parallel follow-up of patients with dry pleurisy suggested that this condition was frequently non-tuberculous.

### TUBERCULOSIS IN GERMAN CONCENTRATION CAMPS AND AMONG PRISONERS-OF-WAR

Surveys of war-time prison camps in Germany left no doubt of the very high incidence of tuberculosis there. Thus, among the survivors in Belsen concentration camp in 1945, the proportion of subjects with pulmonary tuberculosis was estimated at 20–40 per cent. (Lipscomb, 1945; Mollison, 1946). Examination of Allied prisoners in German prisoner-of-war camps, made by Dr. A. L. Cochrane (1945) while himself a prisoner, showed that the prevalence of pulmonary tuberculosis exceeded that to be expected in a male population of similar age constitution; it was highest among the Russians, next highest among the French and lowest among the British. In one area information was available on the rate of reappearance of pulmonary tuberculosis after a large number of prisoners had been X-rayed in 1943; the large international differences were confirmed. These differences were probably associated more with the diet and living conditions of the three groups than with any genetic factors. Thus, the British had the best living conditions and the Russians the worst, and the Russians were given lower rations for the same type of work and received no Red Cross parcels. There was evidence, therefore, that the abnormally high incidence of tuberculosis among the heterogeneous population of young adults in the prison camps was attributable to the operation in extreme degree of some of the same aetiological factors as had contributed to the increased death-rate from tuberculosis among civilians in the United Kingdom at the beginning of the war.

### THE MURINE TYPE OF TUBERCLE BACILLUS (THE VOLE ACID-FAST BACILLUS)

Research aimed at producing a new protective vaccine against tuberculosis was carried out in Great Britain during the war, though it did not reach the stage of large-scale field application. In 1937 Dr. A. Q. Wells, working at Oxford, had isolated from voles an acid-fast bacillus of unusual interest. This differed in certain features from the human and bovine types of tubercle bacillus, and it has since been recognised as a third mammalian type—the 'murine' type. Observations on guinea-pigs showed that infection with this organism conferred a significant degree of protection against subsequent inoculation with virulent human or bovine tubercle bacilli. The possibility arose, therefore, that the murine type of bacillus might be suitable for use as an immunising vaccine in man—that it might, indeed, have certain advantages over the well-known B.C.G. vaccine. Accordingly, Dr. Wells carried out a pilot investigation on human subjects, the result of which was to show that living murine bacilli in suitable dosage could be inoculated by the multiple puncture method into the skin of tuberculin-negative

reactors without giving rise to any general disturbance or serious local inflammation; subjects inoculated in this way became tuberculin-positive as rapidly as after inoculation with B.C.G. (Wells and Robb-Smith, 1946). A comparative trial of the two vaccines for the protection of children of school-leaving age has been organised by the Medical Research Council since the end of the war.

## Influenza

The possibility of a major epidemic of influenza such as had occurred in 1918–19 was an ever-present threat throughout the war, though fortunately it did not materialise. Research on the subject was accordingly continued as part of the war-time programme of the National Institute for Medical Research, where the influenza 'A' virus had been identified in 1933. Garglings and serum samples from patients with influenza were examined in order to determine the nature of the infection prevalent each year. In 1940 American workers discovered a new virus strain, serologically unrelated to the original strain 'A'. Examination of sera held at the Institute showed that some of the influenza in the United Kingdom in the spring of 1939 must have been caused by the newly identified 'B' strain. In the winter of 1939–40 studies were difficult owing to dispersal of the Institute's staff on other duties, but one virus 'A' strain was recovered from material sent from Flanders. In the winter of 1940–1 a big epidemic was expected in England, both on the basis of epidemiological observations of the periodicity of the disease and because the conditions of overcrowding in air-raid shelters at that time seemed likely to favour its spread. Only a minor epidemic developed, however; the 'A' virus was responsible for a large part of this, but the viruses recovered were of low pathogenicity to animals (Andrewes *et al.*, 1941). No influenza appeared in the following winter; but in that of 1942–3 another minor epidemic occurred. Virus 'B' seemed to be the agent chiefly responsible (Stuart-Harris, Glover and Mills, 1943), but at the end of the spring, and through the summer, local outbreaks due to strain 'A' were recognised in East Anglia, Scotland and Northern Ireland. These led up to the only considerable war-time epidemic of influenza in Britain, the 'A' epidemic of October to December, 1943 (Andrewes and Glover, 1944); even this was not very severe, and no further epidemic occurred during the war. The influenza periodicity apparently established before the war was upset, with the fortunate result that epidemics were rather less frequent during the war than before it.

In 1940 a complex vaccine was reported from the U.S.A. to have promise against influenza, and, through the generosity of the Rockefeller Foundation, several hundred thousand doses were provided for trial in Great Britain; 193,900 doses were distributed to the Services for tests in 1940–1, but no influenza occurred in the inoculated groups to

enable a decision to be reached as to the efficacy of the vaccine. Later, work in America threw doubt on the value of this particular vaccine, but another type, developed later, was thought to have given much better results there. It was subsequently tried in Great Britain, but the results were equivocal.

The work on air hygiene discussed in Chapter 6 is also relevant to the control of influenza outbreaks. It has been shown that experimentally produced mists of influenza virus will infect ferrets, and there is some evidence that air-borne 'droplet-nuclei' may convey the virus from an infected ferret to a normal one several feet from it (Andrewes and Glover, 1941). Ultra-violet light (Edward, Lush and Bourdillon, 1943), sodium hypochlorite (Edward and Lidwell, 1943) and propylene glycol aerosols have been found experimentally to be capable of destroying influenza particles in such mists. Edward (1941) and others have demonstrated that influenza virus can persist for a fortnight on dust.

For a more general account of war-time researches on influenza—including Burnet's work in Australia on the cultivation of the virus in chick embryos and the important discovery, made independently by Hirst in the United States and by McLelland and Hare in Canada, of a method of titrating the virus through its agglutinating action on fowl red cells—reference should be made to the article on influenza in Chapter 25 of the volume of this History dealing with Medicine and Pathology.

### Infective Hepatitis and Serum Jaundice

Epidemics of jaundice among Service personnel were so common during the war as to constitute a serious problem for the military authorities. Among the British troops in the Mediterranean area there were 4,000 cases in 1941–2 and 12,000 in 1942–3. A large-scale outbreak occurred in 1942 among American troops who had recently arrived in Northern Ireland; this, like certain smaller outbreaks during the war, was afterwards shown to be due to inoculation of the troops with yellow fever vaccine suspended in a minute amount of human serum from 'jaundice carriers'. At about the same time it was noticed that jaundice was becoming increasingly frequent in patients under treatment at V.D. clinics, and that it might also follow the transfusion of serum or plasma (see Chapter 3). These events gave rise to anxiety about the possibility of even larger epidemics in the Services, spreading also to the civilian population. Consultations between the Ministry of Health, the War Office and the Medical Research Council led, in May 1943, to the appointment by the Council of a Jaundice Committee (Appendix I) and a Jaundice Research Team. The team was under the general direction of Professor S. P. Bedson, and consisted of a bacteriologist (Dr. F. O. MacCallum), a biochemist (Dr. M. R. Pollock), a clinician (Major Clifford Wilson), a clinical pathologist (Captain J. A. R. Miles)

and an epidemiologist (Dr. A. M. McFarlan). It was decided to concentrate the work in the United Kingdom, rather than to send the investigators overseas, where research facilities—including the opportunities for using human volunteers—might be less satisfactory. The team was housed in the Department of Pathology, University of Cambridge, and eventually jaundice was made notifiable in Civil Defence Region IV, which included Cambridge and had a population of 2,650,000. Under this arrangement there was ample clinical material available for study.

In the early years of the war a number of different forms of jaundice were recognised as producing similar clinical and morbid anatomical appearances. These were sporadic catarrhal jaundice at home, epidemic jaundice at home, epidemic jaundice overseas, post-vaccinal jaundice, homologous serum jaundice and post-arsenical jaundice. As the result of investigations by workers in this country and abroad, it is now known that the first three are identical and constitute 'infective hepatitis'; the second three are identical and constitute 'homologous serum jaundice'. Both these diseases are due to virus infection, but there is reason to believe that the viruses are distinct though probably related.

The studies of the epidemiology of infective hepatitis carried out by the Jaundice Team in East Anglia began after the incidence of the disease in that area had reached its peak, but the figures subsequently collected for 1944–5–6 suggested a seasonal trend, with (usually) a maximum incidence in the autumn-winter period. There was a fall in the total incidence in the Region in the last two years of the war, followed by a slight rise in 1946. In the civilian population the incidence rate was 0·5 to 2 per 1,000 population, though this increased to 55 per 1,000 in children of school age in one outbreak; children aged 5 to 14 were particularly susceptible, but the disease, at least in its icteric form, was rare in children under five. The geographical distribution of the disease in the Region in successive years suggested that it had spread centrifugally from London. Studies were also made of outbreaks that began in certain military units of the British Army in Sicily and continued after their return to Great Britain some months later (McFarlan, 1945). These outbreaks were very similar to those occurring in the civil population, with numerous instances of twenty- to forty-day intervals before the onset of illness in contacts. The attack rate in troops in the Mediterranean area was higher than in troops in Great Britain, but there was nothing to show that the 'Mediterranean' strain of virus was more pathogenic or infective than other strains. There was no evidence of spread of infection by water, milk or food. McFarlan and Pollock studied a large outbreak in an institution for mental defectives, where Pollock, using various techniques for the detection of liver damage, was able to diagnose cases as early as ten days before the onset of jaundice, while the total serum bilirubin was still normal

(Pollock, 1945); by using Hunter's test for bilirubin in the urine of contacts in a nursery outbreak, he found a very small proportion of completely symptomless cases of hepatitis. Abnormal results with the bromsulphthalein excretion test were the earliest constant abnormality: one patient showed abnormal retention of the dye when first tested sixteen hours after the onset of symptoms. These studies also facilitated the collection of material from patients early in the disease for transmission experiments in animals and in man.

The investigation of the aetiology of infective hepatitis proved most arduous. Many species of animals were used, as well as every procedure known by pathologists to increase susceptibility to viruses, but, in spite of some promising results in rats on deficient diets, transmission to animals had not been achieved with certainty by the end of the war. It was therefore necessary to use human volunteers. The choice of suitable subjects for the purpose was difficult, because the incubation period of infective hepatitis and the duration of illness were both known to be long, and experimental production of the disease involved some risk both to the individual and to the community. In the United Kingdom, although a small number of conscientious objectors volunteered for transmission experiments, the major source of supply consisted of patients with rheumatoid arthritis. It was already known that the symptoms of rheumatoid arthritis are sometimes relieved by an attack of jaundice, and patients were therefore invited to volunteer with the twin objects of discovering whether jaundice could be transmitted, and whether jaundice so induced would in fact relieve rheumatoid arthritis. Among some 400 volunteers inoculated, of whom 350 were patients with rheumatoid arthritis, jaundice developed in about 10 per cent. It was confirmed that the signs and symptoms of rheumatoid arthritis were often much relieved by an attack of jaundice, but unfortunately the remission was only temporary (Gardner, Stewart and MacCallum, 1945). Though jaundice is a useful research 'tool' for the study of rheumatoid arthritis, it was clear that it could not be recommended as an effective treatment, and the prospect of combining research on jaundice with the large-scale treatment of rheumatoid arthritis had to be abandoned.

The establishment of the aetiology of homologous serum jaundice was rendered difficult by the unusually long incubation period, and its successful achievement was an outstanding event in the medical history of the war. It is now appreciated that jaundice has commonly been the result of therapeutic procedures, particularly the use of inadequately sterilised syringes to give injections, and the way is open for the abolition of this hazard from hospitals and clinics (Salaman, King, Williams and Nicol, 1944; Ministry of Health, 1945; Medical Research Council, 1945). As indicated in Chapter 3, the chances of homologous serum jaundice being conveyed by a transfusion of whole blood from a single

donor are numerically very small. Means of eliminating the infective agent from pooled human serum or plasma used for therapeutic purposes had not been found by the end of the war, but since it was clear that only comparatively few sera contained the icterogenic virus, the risk could be reduced by avoiding large-scale pooling.

The two most important discoveries made during the war by members of the Jaundice Team and their co-workers were that a virus is present in the blood in post-arsenical jaundice (MacCallum, 1945) and that virus is excreted in the faeces in infective hepatitis. Experimental transmission of infective hepatitis to volunteers with faecal material was achieved almost simultaneously by MacCallum and Bradley (1944) in the United Kingdom, Havens and others in America, and Findlay and Willcox (1945) in West Africa; Findlay and Willcox also achieved transmission with samples of urine, but it was concluded, on re-investigation, that this was due to the presence of urinary schistosomiasis with haematuria in the West African soldiers from whom the samples were obtained (Findlay, 1948). The whole series of observations by investigators in the United Kingdom, the United States, West Africa and elsewhere has now given a consistent picture of the distribution of the virus in infective hepatitis and homologous serum jaundice, and of the probable routes of infection. The results support clinical and epidemiological observations to the effect that infective hepatitis may be an excremental disease, spread by contact with contaminated fingers or by flies or, occasionally, contaminated water, though the opinion of the majority of workers is that in this country it is probably more often droplet spread from the pharynx. Attempts to develop a serological test for the presence of the infection were inconclusive. The difficulties due to lack of a susceptible animal must again be emphasised. Without such an animal it proved impossible to bring the research to the final goal of a prophylactic vaccine. Nevertheless, it should be mentioned here that American workers had very encouraging results in the prevention of jaundice by the use of gamma globulin as a protective agent.

The clinical and epidemiological studies of jaundice made during the war are of great interest to physicians and hygienists, but they are too extensive for summary here. Much of the epidemiological work was naturally carried out by the Services, but a close liaison was established between the workers at home and overseas, and the Jaundice Committee proved a valuable agency for assessing and diffusing information as it became available. Two striking phenomena in jaundice in the Services were the high attack rate in officers and flying personnel as compared with ordinary ranks and ground staff; and the low attack rate, but high mortality, in coloured troops. The former phenomenon remained unexplained, the latter may have been due in part to differences of diet. Assessment of various laboratory tests showed that Hunter's test for

bile in the urine was of much value in detecting cases in the pre-icteric stage as well as latent cases; the bromsulphthalein test and the erythrocyte sedimentation reaction might also help in diagnosis during the pre-icteric stage. Hepatic function tests are otherwise of little value in acute hepatitis.

Needle biopsy of the liver was of signal service in delineating the pathological changes in this organ. Dible, McMichael and Sherlock (1943) put beyond doubt the diffuse inflammatory character of the liver lesions in infective hepatitis and homologous serum jaundice. They demonstrated the transitions which might occur to acute liver necrosis on the one hand, and cirrhosis of the liver on the other. Although the vast majority of cases healed completely, in some healing was prolonged, with troubles from residual scarring of the liver. Patients frequently remained sick for lengthy periods after the jaundice had disappeared. Sherlock and Walshe (1946) showed that in spite of continuing symptoms many of these patients were completely normal both by biochemical testing and histological examination of the liver; they suggested that some of them had a 'hepatic neurosis' as a result of creation of anxiety by overmuch medical interest in their problems. In others, however, true hepatic cirrhosis developed, which might run a serious course but on occasions was apparently quiescent for years (Sherlock, 1948). Although needle biopsy has some risks, these are now well defined, and with appropriate precautions the procedure has taken a place in the investigation of obscure liver disorders.

To assess the value of a given line of treatment in diseases so variable as infective hepatitis and homologous serum jaundice, a large sample of cases must be taken and an equally large number of controls. Objective criteria of comparability and of recovery are fairly easily established, but they demand long periods of observation. For these reasons the majority of the therapeutic trials during the war were carried out in home hospitals, as it was rarely practicable to secure adequate conditions overseas. The work of Whipple and his colleagues, of Himsworth and Glynn (1944) and others made it worth while to test whether these acute diseases of the liver could be rapidly improved by dietary treatment, but the results of clinical trials carried out on strict statistical lines were, unfortunately, almost completely negative (Peters, Thompson, King, William and Nicol, 1945; Wilson, Pollock and Harris, 1945, 1946; Higgins, O'Brien, Peters, Stewart and Witts, 1945). There was no difference in response whether the protein or the fat content of the diet was high or low, nor was the value proven of lipotropic substances, such as methionine and choline, though there was a suggestion that cysteine had some therapeutic effect.

In reviewing his experience of infective hepatitis and syringe-transmitted hepatitis in West Africa, Findlay (1948) suggested that the high case-fatality rates from hepatitis in native troops might have been

related to previous liver damage caused by malnutrition, especially protein deficiency. It is possible, therefore, that in such cases dietetic treatment would be of value, even though it has not been shown to have any specific effect in the well-nourished.

The studies of infective hepatitis made in the United Kingdom by the Jaundice Team have been described in detail in a monograph issued by the Medical Research Council since the end of the war (MacCallum, McFarlan, Miles, Pollock and Wilson, 1951). Further accounts of war-time advances in knowledge of infective hepatitis and related conditions are contained in Chapter 9 of the volume of this History dealing with Medicine and Pathology.

## Malaria

Malaria presented a serious problem in the early stages of the campaigns in the South-west Pacific area, South-east Asia, the Middle East, Sicily and Southern Italy. Casualties from this source were exceedingly heavy, and the establishment of effective malaria control became urgent. Special research programmes on malaria were initiated in Great Britain, Australia and the United States, in extension of work on the subject which had been in progress before the war, and numerous field investigations were carried out by medical officers with the Fighting Services in malarious countries. The aspects of the malaria problem studied may be grouped under four main headings: (*i*) Drugs; (*ii*) Insecticides; (*iii*) Insect repellents; (*iv*) Mosquitoes. For a more general account of war-time advances in knowledge of malaria than is given here, reference may be made to Chapter 7 of the volume of the Official Medical History dealing with Medicine and Pathology.

### DRUGS

At the outbreak of war there were in existence three anti-malarial drugs of importance; quinine, atebrin (now known as mepacrine) and plasmoquine or plasmochin (now known as pamaquin). Pamaquin, and later mepacrine, had been developed by German scientists as a result of the shortage of quinine experienced by their armies during the War of 1914–18. The chief action of both quinine and mepacrine is on the asexual parasites of all forms of malaria. They have some effect on the sexual forms of benign tertian and quartan, but none on those of malignant tertian malaria. They have a suppressive action on all forms of malaria for as long as the drug is taken in sufficient dosage, but they do not prevent relapse. Pamaquin has some effect on the asexual forms of benign tertian and quartan malaria, but practically none on those of malignant tertian. It has a marked destructive action on the sexual forms of malignant tertian malaria, as well as on those of benign tertian and quartan. With certain strains of benign tertian and quartan malaria, pamaquin has a remarkable effect in reducing the relapse rate,

particularly when administered in combination with quinine. It acts as a true causal prophylactic in malignant tertian infections, but only when given in a dosage dangerously large for routine administration.

Even before the Munich crisis it was realised in England that mepacrine and pamaquin would be required in large quantities in the event of a Second World War, and in the summer of 1938 the Secretary of State for War assured the House of Commons that action had been taken to ensure the availability of these drugs on a scale sufficient for military needs should the emergency arise; action had indeed been taken to accumulate reserve stocks of the German products, but before 1942 there was no large scale production of either drug in the United Kingdom or in the U.S.A. The capture of Java by the Japanese in that year cut off the supply of quinine to the Allied countries, and rendered imperative the manufacture of the synthetic anti-malarials on a greatly enhanced scale. Steps were taken to produce mepacrine in large quantities in England and the technical details of its manufacture, which had been worked out in the United Kingdom, were made available also to firms in America. Tests carried out early in the war at the Liverpool School of Tropical Medicine had shown that the British-made synthetic anti-malarial drugs were identical in action and toxicity with their German prototypes. During the tests with pamaquin on monkeys infected with *Plasmodium knowlesi* (Adams, Fulton and Lumsden, 1940), it was found that the parasites had developed resistance to the drug (Fulton and Yorke, 1941). It is believed that this was the first unequivocal demonstration of acquired drug resistance in a malaria parasite, and it is of special interest in relation to the question of drug resistance in human malaria, which has become recognised as a problem of widespread practical significance since the end of the war.

While the success of British manufacturers in producing adequate supplies of mepacrine and pamaquin under war conditions was of immense value from the point of view of military medicine, there was general agreement that both mepacrine and pamaquin fell short of the requirements of an ideal anti-malarial drug in many important respects. Accordingly, at the instigation of the Medical Research Council, a conference was arranged in March 1943, between representatives of the Council, the Therapeutic Research Corporation of Great Britain, and Imperial Chemical (Pharmaceuticals) Ltd., to explore the possibilities of developing a more effective compound. A joint programme of research, based on important discoveries already made in the Imperial Chemical (Pharmaceuticals) laboratories, was then worked out by a panel of the Council's Chemotherapy Committee and representatives of the firm. At the same time there was established a regular interchange of confidential information on anti-malarial drugs between groups of workers in academic and commercial laboratories in Great Britain and in the U.S.A., through the agency of the Medical Research Council on

the one hand and the Committee on Medical Research of the Office of Scientific Research and Development (U.S.A.) on the other. Laboratory researches on the properties of synthetic anti-malarial drugs, which had been initiated several years earlier under the auspices of the Chemotherapy Committee of the Medical Research Council, were continued during the war by Dr. Ann Bishop at the Molteno Institute, Cambridge; Dr. Bishop's war-time activities included the preparation of a comprehensive monograph on the use of avian malaria for testing purposes (Bishop, 1942). A number of the drugs examined at Cambridge had been synthesised at the National Institute for Medical Research by Dr. H. King and Dr. T. S. Work (1940, 1942), who also succeeded later in establishing the identity of the German drug 'Sontochin' (SN 6911), stocks of which were captured by the Allies during the campaign in North Africa.

In August 1943, the Medical Research Council appointed a Malaria Committee composed of representatives of the Fighting Services and of academic workers in malariology, pharmacology, entomology and chemistry (Appendix I). Its programme of studies was directed chiefly to the clinical aspects of malaria, including individual prophylaxis. In the same year, as the result of alarming reports regarding the alleged acute toxic effects of mepacrine as used in prophylaxis by the forces in North Africa, the Army authorities set up a special Malaria Research Unit as part of the Directorate of Biological Research, War Office, to examine this problem. This Unit, under the direction of Lt. Colonel B. G. Maegraith, was located at Oxford, in various laboratories of the University. Over 200 students and a number of volunteers from Army units assisted in this investigation by taking mepacrine over extended periods and by submitting to detailed laboratory observations (Maegraith and Havard, 1945). Other researches on similar lines were undertaken at the Royal Army Medical College, Millbank. The chronic toxicity of mepacrine was studied both at Oxford and at Millbank, and it was shown that 100 mg. of the drug could be administered over long periods without producing toxic effects on the liver or other organs (Army Malaria Research Unit, Oxford, 1945, 1946; Drew and Reid, 1945).

Methods for the estimation of mepacrine in the blood and plasma which had been developed in the U.S.A. were adapted by workers in Great Britain for field use with such apparatus as was available. Simplified techniques for estimating the concentrations of mepacrine in blood and urine were devised by King and Gilchrist (1945) and Yudkin (1945). Field trials of these methods were carried out in Italy.

It had been shown in the U.S.A. that in persons taking a daily dose of 100 mg. mepacrine, the maximal plasma concentration was not reached until about six weeks after the commencement of drug

administration. These findings were confirmed and extended at Oxford and at Millbank (Army Malaria Research Unit, Oxford, 1946). The degradation products of mepacrine were studied at Oxford by Hammick and others (Hammick and Firth, 1944; Hammick and Mason, 1945).

In 1943, an important series of experiments was conducted at Horton Hospital, Epsom, by Major K. Mellanby, Major J. Reid, Dr. W. D. Nicol and Mr. P. G. Shute. Thirty-two volunteers took part in these trials, the results of which demonstrated the efficacy of mepacrine in the prophylaxis of malaria. The mosquitoes used for the work were bred at the Malaria Laboratory of the Ministry of Health, at Horton. In the same year, special teams were sent to Italy to determine whether the high incidence of malaria among troops on mepacrine prophylaxis was due to inadequacy of the dosage employed or to failure to take the drug regularly as prescribed. It was concluded that the break-throughs were due to the latter cause. The more rigid enforcement of anti-malaria discipline which followed this report brought about a striking reduction in the malaria rate.

The Army authorities carried out a series of therapeutic trials at a number of centres in England, to compare the value of various mepacrine courses with the combined standard treatment of quinine, mepacrine and pamaquin. Similar trials were arranged in West Africa (Findlay, Markson and Holden, 1944 *bis*; Findlay and Stevenson, 1944) and in the South-east Asia Command (Rogan and Coombes, 1945). The results showed that mepacrine was as effective as quinine in the treatment of benign tertian malaria and more effective in the treatment of malignant tertian, provided that sufficiently large 'loading' doses were given on the first day or first two days. Special trials were also arranged in military hospitals at Colchester, Oxford, Hatfield and Halton to re-appraise the value of a combined quinine-pamaquin course in preventing relapse in benign tertian infections, as advocated by Sinton and Bird in India in 1928 and subsequently found effective in the treatment of U.S. troops stationed in Panama. The results confirmed the earlier opinions that this treatment was more effective than a standard mepacrine course in reducing the relapse rate.

The most comprehensive series of prophylactic and therapeutic trials of anti-malarial drugs conducted during the war period was that undertaken by Brigadier N. Hamilton Fairley and his colleagues at the Australian Army Medical Research Unit, Cairns, Queensland, which was established in June 1943 (Fairley, 1945). More than 800 volunteers drawn from various military units took part in these experiments. Although the outstanding achievement of the Unit was to establish the value of mepacrine in curing *P. falciparum* infections and suppressing *P. vivax* infections, other known or potential anti-malarial agents were also tested, including some of the newer sulphonamides; these were found to suppress and cure *P. falciparum* infections, but they did not

suppress heavy *P. vivax* infections. It was conclusively proved that all types of malaria encountered in New Guinea could be effectively suppressed by the administration of one tablet (100 mg.) of mepacrine daily. The great importance of the Cairns work was the demonstration, accepted without reserve by the General Staff, that the outbreaks of malaria which occurred particularly during a period of active operations were due, not to the direct effect of stress and strain, but to the fact that, under such conditions, anti-malaria discipline was apt to be relaxed so that the drug was not taken regularly. Two other important points demonstrated were that one tablet of mepacrine could be taken daily over an indefinite period without harm and that men taking this dosage regularly could not infect mosquitoes feeding on them. The incontestable evidence produced at Cairns resulted in the issue of drastic orders by the Commander-in-Chief, placing the responsibility of enforcing anti-malaria discipline on the commanding officers of all military formations, who were given clearly to understand that laxity in such discipline would involve instant loss of their command. The more rigid enforcement of drug prophylaxis as well as of all other anti-malaria precautions resulting from this order was followed by a dramatic fall in the malaria rate. Similar steps were taken by the U.S. Army authorities operating in the South-West Pacific area, with equally impressive results. Moreover, the influence of the Cairns experiments was not limited to this area alone. Following a report by Major General Sir Gordon Covell, Consultant Malariologist, India Command, who visited the Research Unit at Cairns and the Australian and U.S. military formations in New Guinea in 1944, equally drastic regulations were enforced throughout the South-east Asia Command, with a corresponding effect on the malaria rate in that area.

Fairley and his colleagues subsequently carried out trials on similar lines with proguanil ('Paludrine'), a new biguanide compound developed in the laboratories of Imperial Chemical (Pharmaceuticals) Ltd., which had been favourably reported on by Lt. Colonel Maegraith and Dr. A. R. D. Adams at the Liverpool School of Tropical Medicine (Curd, Davey and Rose, 1945; Adams, Maegraith, King, Townshend, Davey and Havard, 1945). The derivation of this drug from the earlier pyrimidine analogues, and these in turn from mepacrine, has thrown some light on a possible relation between chemical structure and anti-malarial activity. In this research it was suggested that the tautomeric possibilities inherent in mepacrine might also be exhibited by a similarly substituted pyrimidine; the latter nucleus was selected for study as being non-chromophoric and because of its significance in biological chemistry. The introduction of amino, or substituted amino groups, together with methyl groups, led to the production of substances active against the erythrocytic forms of avian malarias. Further consideration of the tautomeric possibilities indicated that the essential

features presented by the pyrimidine ring might also be shown by the related acyclic biguanide system. This line of reasoning ultimately led to the development of proguanil. The work at Cairns showed that this drug possessed certain important advantages over other anti-malarials, notably in regard to its action as a causal prophylactic in malignant tertian malaria, its effect in sterilising gametocytes and its low grade of toxicity. Proguanil, however, did not come into general use until after the termination of hostilities; nor did chloroquine (SN 7618), which was subsequently adopted as a standard anti-malaria treatment in the U.S. Army, on the basis of extensive tests confirming earlier work in Germany. Throughout the war period, therefore, mepacrine continued to be the mainstay in the prophylaxis and treatment of malaria in all areas where the disease was a problem of military importance. A full description of the work done by Hamilton Fairley and his colleagues at Cairns will be found in the Australian *Medical History of the War*, Volume I, Chapter 7.

### INSECTICIDES

During the three-year period immediately preceding the outbreak of war, the destruction of adult mosquitoes by the spraying of insecticides had become recognised as one of the most effective of all anti-malaria measures. It is particularly appropriate for use under conditions of active warfare, as for instance immediately after the capture of an enemy position, or the occupation of a village likely to harbour infective mosquitoes. Pyrethrum was the active ingredient of most of the insecticides in use at the outbreak of war. A great part of the world's supply of pyrethrum flowers came from Dalmatia and Japan, and after the entry of the latter country into the war the sole source of supply remaining to the Allies was Kenya, whose total output was insufficient even for their normal peace-time agricultural needs. Research programmes were therefore initiated in the U.K. and in the U.S.A. with the object of discovering an efficient substitute for pyrethrum. A very large number of substances were investigated, the most important being dichlorodiphenyl-trichlorethane (D.D.T.), which had been synthesised by a German chemist in 1874. It was not until 1939, however, that the remarkable insecticidal properties of this compound were discovered, when, as the result of work in their Basle laboratories, the Swiss Company of Geigy reported it to be effective against clothes moths, flies in stables and certain agricultural pests. D.D.T. was introduced into the U.K. and U.S.A. towards the end of 1942, and early in 1943 a further report was received from Basle that it had been found exceedingly effective against the body louse. At this stage an Insecticides Development Panel was set up under the chairmanship of Professor (now Sir) Ian Heilbron, Chemical Adviser to the Ministry of Production, and intensive research was instituted with the object of producing

D.D.T. on an extensive scale and of testing the various preparations—powders, solutions, emulsions and suspensions—by which it might be applied to the best advantage. In April 1943 the first batch of D.D.T. was produced on the pilot plant in the Geigy laboratories at Manchester, and in November of that year the first bulk production was achieved as the result of a co-operative effort between engineers, chemists, industrialists, biologists and government officials. Researches on the insecticidal properties of D.D.T. were carried out at the London School of Hygiene and Tropical Medicine (Buxton, 1945), while parallel tests of its toxicity were made at the Chemical Defence Research Experimental Station, Porton.

The first full-scale use of D.D.T. in a war sector was against the louse in the Naples epidemic of typhus early in 1944. Field trials with this insecticide against mosquitoes were conducted in India in 1944, and it was used on a wide scale during the later stages of the campaign in Burma, being applied from aircraft as well as by anti-malaria units operating on the ground. It was also used during this period in the South-west Pacific area, particularly by the U.S. forces. It should be noted, however, that the malaria rate in that area had been brought down to insignificant proportions before supplies of D.D.T. became available.

Another insecticide, in some respects more powerful than D.D.T., was developed during the war in the laboratories of Imperial Chemical (Pharmaceuticals) Ltd. This was gamma benzene hexachloride ('Gammexane', or B.H.C.). The activity of this substance as an insecticide was discovered in 1942, but certain difficulties were encountered in its manufacture and purification, and during the war years attention was focused chiefly on the development and method of application of D.D.T. 'Gammexane' was not available for general use until after the termination of hostilities.

### INSECT REPELLENTS

In the early stages of the war, a citronella cream which had been used for many years by field units of the Malaria Institute of India was supplied to the Army. This proved too greasy for men engaged in heavy work under tropical conditions, and, moreover, the demand for a repellent was so great as to result in an acute shortage of oil of citronella. Investigations were made by Sir Rickard Christophers in England and by a team of workers at the Orlando laboratories of the U.S. Bureau of Entomology and Plant Quarantine, with the object of developing an improved type of repellent for use in the field. A very large number of substances and vehicles for application were studied. Many of these had strong repellent properties, but in most cases there were difficulties in securing their production on a sufficiently large scale. Dimethyl phthalate proved the most useful for protection against Anopheles mosquitoes, since it was not only an effective

repellent but was also available in large quantity. For general use against all types of insects, a mixture of dimethyl phthalate, 'Rutger's 612' and indalone, known as '6-2-2 mix' from the proportions of each ingredient, was adopted as a standard issue to the U.S. forces.

Field and laboratory researches on repellents and their application were carried out by the Malaria Institute of India and by anti-malaria units in the South-east Asia Command. One of the more important developments in this area was the demonstration of the efficacy of wide mesh fish netting soaked in dimethyl phthalate in greatly prolonging the period of effective repellency. Veils, gauntlets and stockings of this material were supplied to certain units in the Command and proved exceedingly effective.

Researches on the protective effects of various types of clothing material were also undertaken by Sir Rickard Christophers in England, by workers in the U.S.A., by the Malaria Institute of India and by anti-malaria units of the South-east Asia Command.

### MOSQUITOES

In many of the highly malarious combat areas, e.g., New Guinea, the Assam-Burma border, Iraq and Eritrea, knowledge regarding the bionomics and in some cases even the identity of the vector species of Anopheles was incomplete at the start of military operations. During the war much valuable research was carried out by officers attached to malaria field laboratories and anti-malaria units, which served to clear up the various problems at issue and greatly facilitated the operation of mosquito control measures. Particularly useful work in this direction was done by Lt. Colonel I. M. Mackerras, Captain F. M. S. Roberts and Major A. R. Woodhill with the Australian forces in New Guinea, by Major C. R. Ribbands and Dr. R. C. Muirhead Thomson in West Africa, by Lt. Colonel D. Bagster Wilson and his unit in East Africa, and by Major Leeson, Lt. Colonel W. H. R. Lumsden, Lt. Colonel J. Yofe and Major T. T. Macan in the Near East.

From studies of *Anopheles melas*, first clearly differentiated in its breeding habits from *A. gambiae* by Ribbands and Muirhead Thomson, were developed the distinctive methods of control by bunding in the brackish mangrove areas, which were used extensively by Gilroy and by Tredre in West Africa.

### BLACKWATER FEVER

The most striking feature of blackwater fever observed during the war was its virtual disappearance from European troops in West Africa after mepacrine had been substituted for quinine in the suppression and treatment of malaria, in 1943.

African troops did not take suppressive drugs, since Africans from the areas where they were recruited possess considerable immunity to

*Plasmodium falciparum* and the other malaria parasites. Immunity in malaria, however, depends for its maintenance on superinfection at frequent intervals, and these troops were removed from their own habitual surroundings to places where efforts were made to reduce the frequency of exposure to bites of infected mosquitoes. It was observed that the incidence of blackwater fever, which is rare in Africans living under their habitual conditions, increased in these troops as time passed, and it is inferred that a reduction of immunity, together with occasional exposure to infection with *P. falciparum*, produced the state of sensitisation which increased the chance of blackwater fever in troops not taking suppressive mepacrine. If this assumption is correct, it has a bearing on attempts to reduce the transmission of malaria in African communities in peace-time.

The relevant figures of incidence of blackwater fever are as follows (Findlay, 1949): some 50,000 European and 250,000 African troops were concerned:

*Incidence of Blackwater Fever in European and African Troops in West Africa* 1941-1945

| Year | *Europeans* | | *Africans* | |
|---|---|---|---|---|
| | No. of cases | Rate per 10,000 strength per annum | No. of cases | Rate per 10,000 strength per annum |
| 1941 | 36 | 56·1 | 1 | 0·23 |
| 1942 | 102 | 82·9 | 6 | 0·68 |
| 1943 | 39 | 30·6 | 13 | 1·30 |
| 1944 | 2* | 2·3 | 36 | 5·49 |
| 1945 | 0 | — | 66 | 12·77 |

* Includes one doubtful case of haemoglobinuria associated with peritonitis and *Clostridium welchii* infection.

Research into the fundamental problems of blackwater fever has long been carried out, notably by Foy and Kondi and their associates in Greece just before the war; their work was continued in Africa during the war. Like other workers, Foy and his colleagues sought a haemolytic agent in the blood of patients with blackwater fever, and they found evidence that a lytic principle exists, which may be lysolecithin (Foy and Kondi, 1943).

In West Africa, during the war, Maegraith, Findlay and Martin (1943) took up the study of blackwater fever, but they came to a different, and new, conclusion. Animal tissues contain a heat-labile lytic agent, but this is normally inhibited by factors which have been found in tissue washings, and in serum. Sera from patients with blackwater fever, however, are much less effective than normal sera in inhibiting the lytic agent. These authors concluded that in blackwater fever there is no abnormal lysis, but that the lysis is simply a manifestation of excessive uninhibited activity of the normal lytic process.

Maegraith and Findlay (1944) showed that the deciding factor in the oliguria and anuria of blackwater fever is not blockage of the renal tubules by haemoglobin products, and subsequent work by Maegraith and his colleagues suggests that the basis of the renal failure is anoxia resulting partly from the malarial anaemia and partly from reduction in the effective tubular blood supply brought about by changes in the intra-renal blood flow, associated with peripheral vascular disturbances of a general nature (Maegraith, 1944, 1946). Experimental work in dogs suggested that the degree of anoxia in blackwater fever depends on the rapidity and extent of the haemolysis, and on the condition of the blood before the haemolysis begins (Dawson and Findlay, 1947).

In 1942 Mobile Blackwater Fever Teams were formed in West Africa (Findlay, 1943). Each team was based on an army hospital, and consisted of a medical officer, a nursing sister, and orderlies, with full equipment. Orders were issued that patients with blackwater fever were not to be moved to hospital but were to be treated where they had been taken ill, and whenever a case of blackwater fever occurred a team was sent out, if necessary by air, to treat and nurse the patient on the spot.

The work of the investigators in West Africa, especially Maegraith, on the treatment of blackwater fever led them to issue a warning against the indiscriminate administration of alkalis if kidney function is deranged. They question the basic hypothesis on which the use of large doses of alkalis is founded.

## The Typhus Fevers

### EPIDEMIC (LOUSE-BORNE) TYPHUS AND MURINE TYPHUS

Experience in the War of 1914–18, and in the years following it, suggested the likelihood of extensive outbreaks of epidemic typhus during the War of 1939–45. The remarkable degree of control over this infection achieved by the use of D.D.T. and other insecticides to destroy the louse vector represented an outstanding triumph of preventive medicine. Immunisation with vaccines made by cultivating the rickettsiae in eggs, which was introduced by Cox and Bell in the United States in 1940 and later improved by Craigie in Canada, was also of great value in protecting soldiers and others exposed to the infection against the risk of contracting severe attacks of the disease; though the immunity given by the vaccines available during the war was incomplete, it generally ensured that the attack in an inoculated person was relatively mild.

Prophylaxis of epidemic typhus by D.D.T. and large-scale active immunisation became available only during the course of the war, and at the start of hostilities the disease seemed likely to become a greater menace than in fact it did. For this reason, work on new insecticides against the louse was undertaken intensively by workers in the United

Kingdom and other countries from the beginning of the war, as described under the heading of Medical Entomology in Chapter 6. For the same reason, the laboratory study of typhus became one of the principal war-time activities of the National Institute for Medical Research in London. The investigators there worked in close collaboration with those engaged on similar studies at the R.A.M.C. Emergency Vaccine Laboratory at Tidworth and later at Everleigh, Wilts., and with others undertaking field inquiries with the Army Medical Service in the Middle East and North Africa. In Britain, attention was concentrated on aspects of the problem which were not already being intensively studied by workers in the U.S.A. and Canada; because of the progress already made in those countries with the development of egg-yolk vaccines against epidemic typhus, no large-scale work on the preparation of these vaccines was undertaken in the United Kingdom, where the shortage of eggs would, in any event, have made their mass production difficult. Much work was, however, done at the National Institute on methods of assaying typhus vaccines, and on comparing rickettsial strains obtained from typhus outbreaks in various parts of the world, with a view to ascertaining whether the existing vaccines were likely to be effective wherever they were used.

The undertaking of work on typhus at the National Institute necessitated the adoption of elaborate precautions against the spread of the infection from inoculated animals. At first, work in the Institute was confined to the murine strain of typhus rickettsia and the more dangerous epidemic strain was studied only in special accommodation at the Farm Laboratories of the Medical Research Council at Mill Hill. Later, when the investigators had become familiar with methods of handling the infection, all the work was transferred to the main Institute. There the typhus laboratories formed a self-contained unit; the infected animals were also housed in a separate unit in the animal house, the cubicles of which opened only to an outside balcony. Workers wore special gowns and, for the more dangerous manipulations, masks and gloves. Special methods were devised for safely disposing of all infected material. Despite these precautions, and despite inoculation with the best typhus vaccines then available, five workers at the Institute became infected with murine typhus soon after work was begun in 1942; nine similar infections occurred in the military laboratory at Everleigh. The source of these infections almost certainly consisted of air-borne rickettsiae exhaled by mice which had just been inoculated intranasally (van den Ende *et al.*, 1943). Subsequently, a special inoculation box was constructed so as to ensure that all air leaving the chamber was first sterilised by heat (van den Ende and Hubbard, 1943). Boxes of this type were used in all later work on the subject at the Institute and at Everleigh, and only one laboratory infection with murine typhus occurred thereafter.

For the intranasal infection of mice and other animals with typhus rickettsiae a modification of the technique devised by Burnet and Rudd for studies of psittacosis was successfully used; it was found that mice inoculated intranasally with dilute rickettsial suspensions developed in their lungs discrete grey spots, whose numbers were sufficiently reproducible for accurate quantitative work (spot-count technique). The numbers of spots were reduced in the presence of immune serum, and a 'neutralisation test' for the detection of antibody against the rickettsia was thus available (van den Ende *et al.*, 1946); this gave results of much interest in comparison with other methods of assaying typhus antibodies.

Immunological tests by several methods showed that epidemic typhus strains were antigenically indistinguishable, whether coming from Poland, Russia, Iran, Irak, Egypt, North Africa, Italy, Syria or Palestine; this fact, which was not known for certain before, was important in indicating that one type of vaccine should protect against the disease anywhere in the world. Antigenic studies by Forrest Fulton and A. M. Begg elucidated the relationships between the murine and epidemic types of rickettsiae, and between these and *Proteus OX* 19, the bacillary strain used in the Weil-Felix test. Surface antigens of the epidemic and murine strains of rickettsiae seemed to give rise to a heterogeneous group of antibodies, some of which were strain-specific while others reacted with the other strain. Boiled suspensions acquired a new serological specificity that was the same whichever strain was employed. The *OX* 19 antibody was found to be distinct from those reacting with the undegraded surface antigens, but to correspond to a fraction of the antibody reacting with boiled rickettsiae. These and cognate serological investigations had a valuable practical application in epidemiology, since it thus became possible, even in the cases of vaccinated people, to tell whether an infection was due to the louse-borne or flea-borne (i.e. murine) rickettsiae (van den Ende *et al.*, 1943; van Rooyen and Bearcroft, 1943). Similar results were reported from the United States.

Other studies of the pathology of murine and epidemic typhus made at the National Institute included observations on the inclusion bodies formed in the lungs of infected rodents (Begg, Fulton and van den Ende, 1944), and filtration measurements of the size of typhus rickettsiae (Elford and van den Ende, 1944).

The largest programme of work on typhus undertaken at the National Institute was, however, concerned with the problem of chemotherapy. In the course of these investigations, which involved the examination of some hundreds of compounds from various sources for activity against the causal rickettsiae, two were found to be highly effective in experimental typhus in mice (Andrewes, King, van den Ende and Walker, 1944); these were *para*-sulphonamidobenzamidine hydrochloride (V147) and *para*-sulphonamidobenzamidoxime hydrochloride (V186).

As these compounds were found to have no excessive toxicity for animals or human volunteers, it was considered justifiable to try them in cases of typhus in man. Accordingly, in June 1943, a British Army Typhus Research Team was constituted to undertake clinical trials. The first tests were carried out in civil hospitals in Algiers during the summer of 1943. Earlier in the year, a few cases of epidemic typhus had occurred in Naples; with the beginning of the winter the number of cases notified began to rise, until in December there was a sudden serious increase in incidence. The Typhus Team moved to Naples in January 1944, and there carried out further trials of V147 and V186 until the epidemic began to wane. Unfortunately, both these drugs failed to fulfil the hopes raised by their efficacy in mice; they proved of no practical value in human infections under field conditions. Cases were rarely available for treatment at the early stage in the disease at which, in accordance with the results obtained in experimental animals, therapeutic response might have been expected. When used at the later stage at which most patients came under treatment, there were indications that the drugs in some instances might have accentuated the known liability to kidney damage in severe cases of typhus. The highly specific activity of these compounds against rickettsiae was of considerable scientific interest, but from the practical point of view it is regrettable that the discovery of the antibiotics—chloramphenicol, aureomycin and terramycin—which are now known to be very effective against typhus did not take place until after the war.

A full account of the chemotherapeutic investigations undertaken at the National Institute, and in the field in North Africa and Naples, is given in a Special Report of the Medical Research Council (van den Ende *et al.*, 1946). The report also deals with some of the immunological studies carried out at the Institute. Apart from the scientific results it records, it is of interest in containing what must surely be the fullest description yet published of the clinical and pathological features of louse-borne typhus.

In November 1943, at the request of the War Office, the Medical Research Council appointed a Typhus Research Committee (Appendix I) to co-ordinate the research already in progress at the National Institute with that sponsored by the Army at home and overseas, and to maintain close liaison with workers on kindred problems in the U.S.A. and the Dominions. At first the committee's activities were confined to louse-borne typhus. Work on vaccines for this disease, and on the new delousing powders, was in an advanced stage of development, and the Typhus Research Team was already established in North Africa, when, in December 1943, the work of the committee was greatly extended in response to an urgent request from South-east Asia Command for assistance in combating serious outbreaks of scrub typhus among the troops operating in Burma (see overleaf).

### MITE-BORNE (SCRUB) TYPHUS

Scrub typhus had been known for many years as a disease of Japan and China. It is caused by inoculation with *Rickettsia tsutsugamushi* by the agency of Trombiculid mites; the latter, which are found on the ground vegetation in certain areas, feed predominantly on small rodents. In 1924, workers at the Institute for Medical Research, Kuala Lumpur, identified the disease in Malaya, and it has since been recorded from Assam and other parts of India, Burma, Ceylon, New Guinea, Queensland and a number of other localities in the Far East and South-west Pacific areas. In December 1941, a conference was held in London between representatives of the War Office and the Medical Research Council and the Director of Pathology, Australian Army, as the result of which Dr. R. Lewthwaite, Senior Pathologist, Institute for Medical Research, Kuala Lumpur, was sent to Melbourne to work on the preparation of a vaccine against scrub typhus. When the appeal from South-east Asia Command was received in December 1943, no success had been achieved in the preparation of an effective vaccine, either in Australia or in the U.S.A. The Typhus Research Committee therefore recommended that fresh work on scrub typhus should be initiated at the National Institute, by a method based on the growth of typhus rickettsiae in the lungs of rodents, which had been achieved earlier by Castaneda and others in the cases of murine and louse-borne typhus. This work eventually resulted in the preparation of a vaccine of high rickettsial content from the lungs of cotton rats. Squadron Leader C. D. Radford, an authority on mites, was despatched to an Army Entomological Unit in South-east Asia Command to study the ecology of the mite vectors. Limited supplies of the mite-repellants, dibutyl and dimethyl phthalate, which had proved valuable in the hands of American and Australian workers in New Guinea, were sent to the Burma theatre for further trial.

In the spring of 1944, Dr. Lewthwaite was sent to South-east Asia Command as Field Director of a Medical Research Council Scrub Typhus Commission. The commission reached the headquarters of South-east Asia Command in Ceylon in July 1944. Doubt as to the exact identity of the disease affecting the Allied troops had already been dispelled by the isolation of the causal organism from human cases, and field work by members of the commission in infected areas as widely separated as Imphal in Assam and Addu Atoll in the Indian Ocean repeatedly confirmed the presence on jungle rodents of the known Malayan vector mite, *Trombicula deliensis*; some of these mites yielded strains of *Rickettsia tsutsugamushi*, the causal organism. With a view to extending knowledge of the epidemiology of the disease, a field laboratory was established at Imphal. Here Major K. Mellanby and others carried out detailed studies of the mites, their mammalian hosts,

their botanical associations in infected areas, and other factors of importance in the aetiology of scrub typhus. A field research team of the Medical Directorate, G.H.Q., India, collaborated in these inquiries.

Meanwhile the commission began an active campaign to reduce the incidence of the disease, which had reached alarming proportions. In the period July–October 1944, 3,000 cases occurred in the Fourteenth Army alone, with a mortality of 5 to 20 per cent. Furthermore, ignorance of the rôle of the mite had lent an air of mystery to the outbreaks, so that the troops at risk were unduly alarmed. An immediate requirement was to dispel their exaggerated fears by instruction both on the cause of the disease and on the means of prevention; special film shows and lectures were arranged for this purpose. Preventive measures involved principally the improvement of camp sites so as to make them unfavourable to mites, and the use of protective clothing and mite repellents. Two of the members of the commission visited Dr. R. N. McCulloch in Australia and American workers in New Guinea, to obtain first-hand information of the field use of dibutyl and dimethyl phthalate. For practical reasons the method of McCulloch, using dibutyl phthalate, was considered the most suitable under the conditions obtaining in South-east Asia Command, and the troops were instructed accordingly.

In June 1944, Dr. Forrest Fulton reported to the Typhus Research Committee that the vaccine made from the lungs of infected cotton rats on which he had been working gave a fair degree of protection to mice against scrub typhus in the laboratory (Fulton and Joyner, 1945). A limited trial of the vaccine was begun in the autumn, small amounts being despatched for the inoculation of selected Army units. Before any answer as to the efficiency of the vaccine in man had been obtained, an urgent request was received from South-east Asia Command in November 1944, for one and a half million doses; the dead-line delivery date for the first 100,000 doses was fixed for August 1945. In spite of the lack of positive evidence of protection by the vaccine in man, the Army authorities decided that, in view of the very large number of troops involved and the possibility that the vaccine might save lives, its mass production should be undertaken. Large quantities of the vaccine were prepared by the Wellcome Foundation for the Ministry of Supply, and as the material became available it was sent to H.Q. Allied Land Forces, South-east Asia Command. The abrupt end of the war against Japan prevented assessment by the Army of the efficacy of the vaccine, and need for it has been lessened since the discovery of the antirickettsial action of chloramphenicol, aureomycin and terramycin.

For a more general account of war-time work on the typhus fevers than is given here, reference may be made to Chapter 8 of the Medicine and Pathology Volume.

## The Dysenteries

In the past, gastro-intestinal infections were among the most dreaded afflictions of armies in the field. In the First World War, improved hygienic conditions and the general application of immunisation methods greatly reduced the incidence of the enteric fevers, but the dysenteries proved much more resistant to control measures. Preventive inoculation against bacillary dysentery never proved really effective, and the problem of control was made more difficult because of the high carrier rate and long persistence of the carrier state. Attempts were made in Great Britain and in the U.S.A., both before and during the war, to produce an effective vaccine, but the results on the whole were disappointing. One difficulty was the existence of a multiplicity of types of the causal organism, each of which evokes an immunity peculiar to itself, but is not protective against types of different origin. Moreover, the inherent toxicity of the dysentery bacillus renders the vaccine liable to produce such severe local and general reactions as to make its general application among troops impracticable.

In the early stages of the war, antisera were extensively used in the treatment of bacillary dysentery, most of the successful cases being those receiving a product obtained by injecting the horse with Shiga toxin and then with Shiga and Flexner bacillary bodies. With the introduction of the sulphonamides for the treatment of this disease, serum therapy was almost entirely superseded. A brief account of the use of sulphonamide drugs for the purpose, and of the outstandingly good results achieved, is given in Chapter 7.

Investigations on dysentery were carried out during the war in various military hospitals and in their attached laboratories operating in Egypt, the Sudan, Eritrea, Palestine, Syria, Cyprus, Libya, Cyrenaica, Tripolitania and Malta. From 1940 to 1943 attempts to isolate dysentery bacilli were made as a routine in all suspected cases in these areas. During this period, 64,972 cases of clinical dysentery were investigated, and dysentery bacilli were isolated on 23,951 occasions (Boyd, 1946). Over 94 per cent. of the strains were serologically identified by means of the standard sera supplied by the R.A.M.C. Emergency Vaccine Laboratory. The figures bore a remarkably close relationship to those obtained from a similar survey carried out among troops in India during the period 1932–5:

| | Army in India 1932–5 | Middle East Force 1940–3 |
|---|---|---|
| Shiga | 14·3 | 18·9 |
| Schmitz | 5·5 | 6·7 |
| Sonne | 10·9 | 7·4 |
| Flexner I–VI and Boyd I | 62·3 | 61·6 |

The number of cases in which *Entamoeba histolytica* was isolated was 3,463, which represents 5·33 per cent. of all cases investigated (Boyd, *loc. cit.*).

Amoebiasis became a serious problem during the later stages of the campaign in Burma. Extensive screening studies of possible new amoebicides were carried out in the United States, but they had not reached the stage of practical application by the end of the war. For the treatment of resistant and relapsing cases from the Burma front various 'blunderbuss' courses of treatment embodying emetine bismuth iodide, oxyquinolines and arsenical preparations were tried with varying degrees of success. In intractable cases, invalided home from India, Hargreaves (1945) found that penicillin and succinylsulphathiazole were of value in controlling secondary bacterial infection of the amoebic ulcers and thus improving the chances of subsequent cure by amoebicides. Although this line of attack has not proved universally satisfactory, it has opened a new approach to the problem by emphasising the rôle of factors other than the entamoeba in maintaining resistant infection.

Research on the biology of the intestinal amoebae of man was carried on throughout the war period by Dr. C. Dobell at the National Institute for Medical Research. The life histories of *Endolimax nana* and *Iodamoeba* were the subject of intensive studies and considerable progress was made in the difficult task of defining precisely the conditions required for the cultivation *in vitro* of *Entamoeba histolytica*. Just after the end of the war Dobell succeeded in growing this organism in the presence of a single bacterial species, thus providing the basis of an improved technique for testing amoebicides in the laboratory.

For a more general account of war-time research on the dysenteries, reference should be made to the section dealing with Advances in Tropical Medicine in Chapter 7 of the Medicine and Pathology volume.

## Sprue

A series of studies of this disease was carried out under the auspices of General Headquarters, India Command, on cases occurring during the war among the forces operating in South-east Asia Command and in India itself. Data collected during the early stages of the war confirmed that sprue is a disease in which the faeces contain excessive amounts of fat, most of which is split. At the same time it became evident that random sampling of the faecal fat percentage was by no means a certain method either of diagnosing or of excluding steatorrhoea, since many patients with undoubted sprue were found to have faecal fat percentages within the accepted normal limits. Early in 1945, a Sprue Research Team was established at Poona, with the object of defining the nature of the absorption defect in sprue and of assessing current methods of treatment.

Since the salient biochemical feature of sprue is steatorrhoea, the absorption of fat was more intensively studied than that of other substances (Black, Bound and Fourman, 1947). The methods used included collection of total stools over successive four-day periods, while the patient was on a diet of known fat content; the estimation of blood fat changes after a fatty meal; and the counting of chylomicrons, small fatty particles which appear in the serum after a fatty meal. The fat balance experiments showed that steatorrhoea could be completely abolished by a fat-free diet, indicating that true excretion of fat is not significant in causing the steatorrhoea of sprue. On a diet containing 50 to 100 g. of fat per diem, the failure to absorb fat was only partial; most patients absorbed between 60 and 80 per cent. of the dietary fat. Although these figures might suggest a rather trivial defect in fat absorption, it must be remembered that normal persons absorb more than 90 per cent. of the dietary fat; so that a fat absorption of 70 per cent. means that the stools will contain at least three times as much fat as those of a normal person. During periods of acute diarrhoea, fat absorption in sprue is impaired still further. In the absence of diarrhoea, the fat absorption in any one untreated patient shows little change; the percentage of fat absorption may thus be used in assessing the effect of treatment. Such observations are time-consuming, and it was hoped that blood fat curves or chylomicron counts might provide a quicker assessment of the fat absorption defect. It was found, however, that blood fat curves in sprue often lay within the normal range, which is wide; chylomicron curves were generally normal, except in a few patients with active diarrhoea. A detailed analysis of the fat curves gave some support to the view of Stannus (1942), that neutral fat absorption is not impaired in sprue, but that split fat absorption is diminished; this matter could not, however, be regarded as settled, as the fat curve results were very variable.

Certain cases of sprue, amounting to about 10 per cent. of the total number, presented a special problem, in that they showed a low blood pressure, with signs of dehydration and peripheral vascular failure. In such cases, the serum sodium and chloride were low, and the patients were in fact suffering from salt deficiency, mainly caused by loss of fluid and salt in copious watery stools. Replacement therapy with salt yielded good results in these cases, provided that the diarrhoea was also arrested by sulphaguanidine and by the parenteral administration of crude liver extracts. The fat absorption defect, when measured by balance experiments, proved very resistent to treatment. Even large doses of liver extracts, given by injection, influenced the fat absorption only slowly, though they had a rapid effect in making patients gain weight and feel better. Yeast extract, which could be given by mouth in large doses, appeared to have a greater effect than injected liver extracts in improving fat absorption. Treatment with nicotinic acid

and riboflavin alone did not reproduce the favourable effects of the liver extracts.

A list of publications dealing with studies of sprue by British investigators during the war is given at the end of this chapter; it includes the full report on the work of the Army team in India, published in 1948, but, for the reason given in the Preface to this volume, it does not include the extensive fundamental studies of abnormalities of fat absorption which were carried out by Professor A. C. Frazer and his colleagues at Birmingham during the war and have been continued since. For a more general account of progress in knowledge of sprue and related conditions during the war, reference may be made to Chapter 7 of the Medicine and Pathology Volume.

## Q Fever in the Mediterranean Area

During the winter and spring of 1944–5 several outbreaks of a febrile disease resembling atypical pneumonia occurred among the Allied troops in Italy, Greece and Corsica.

One such outbreak in the Naples-Caserta area was investigated by Caughey and Dudgeon (1947). Altogether 511 cases were reported; 50 consecutive cases were studied in detail. The clinical picture was characterised by a prodromal period of about six days, followed by an abrupt onset with severe headache, malaise, lassitude, anorexia, and fever. In 70 per cent. of the cases the temperature rose to over 103° F.; the fever lasted eight to nine days, and generally terminated by lysis. Cough was almost invariably present but was not severe, and in a quarter of the cases the sputum, which was scanty, contained blood. Severe toxaemia was not uncommon. The lymphatic nodes were usually enlarged, and the spleen was palpable in one-third of the cases. X-ray examination of the chest showed the presence of infiltration localised to one or more bronchopulmonary segments, clearing within six weeks. The true nature of the disease was not recognised at the time, but in the light of work carried out by American bacteriologists, sera from 20 of the patients were examined two years later, and 19 of them were found to contain complement- fixing antibodies to an Italian strain of *Rickettsia burneti*.

The mode of infection and transmission could not be determined, but it is probable that the organism was inhaled in the form of dust, which was abundant in the hay and straw used for bedding. Many of the local civilian population showed a high level of antibodies to the Q fever rickettsia, indicating that the infection was endemic in the area.

## Poliomyelitis in Colonial Territories

In the winter of 1942–3, towards the end of the siege, Malta and the neighbouring island of Gozo were visited by a sharp epidemic of poliomyelitis which affected 426 natives of the island, almost all

children, and 57 men in the Fighting Services, all natives of the United Kingdom. At the request of the Secretary of State for the Colonies, Professor H. J. Seddon went to Malta to assist with arrangements for the care of the civilian cases. The occurrence of the outbreak in an almost completely isolated island community was of considerable interest, but it was impossible in the circumstances to make a complete epidemiological survey. (See The Civilian Health and Medical Services, Volume II, Part I, Chapter 2.)

In the early months of 1945 an epidemic of the disease began in Mauritius, and Professor Seddon, to whom a similar request was again made, suggested that he should be accompanied by an epidemiologist. At the request of the Colonial Office the Medical Research Council arranged for Dr. A. M. McFarlan to be seconded from the Public Health Laboratory Service for a period of three months. The investigators were fortunate in being able to recruit competent medical assistants in East Africa and in Mauritius itself. Two field teams were formed, one epidemiological, the other clinical, and an almost complete survey was made of the thousand or so known cases (McFarlan, Dick and Seddon, 1946). It was concluded that the general character of the outbreak was an epidemic of a disease endemic in the island. A geographical march was clearly demonstrated: the outbreak began in one urban district and spread centrifugally along lines of communication, the infection probably being carried by healthy adult males; a precipitating factor was the occurrence of a cyclone that caused great damage in the first district to be affected and a consequent rapid dispersal of homeless people to various parts of the island. The attack rates in various sections of the population indicated that the chief factor in the spread was human contact, while the rapidity of the spread, and the character of the epidemic curves both for the island as a whole and for individual towns and villages, suggested a spread by transient carriers who became infectious a few days after infection. It seemed likely that there was a widespread carrier epidemic spreading rapidly among adults and children and followed about a week later by a much smaller epidemic of overt poliomyelitis. The incubation period could be computed with fair accuracy and was considered to be eight to fourteen days.

Two other outbreaks of poliomyelitis in colonial islands occurred after the end of hostilities, but since they were almost certainly determined by abnormal circumstances persisting from war-time into the post-war period, they are suitably mentioned here. The first was in St. Helena in the autumn and winter of 1945–6; it was studied by Mr. K. I. Nissen, whose release from the Navy to undertake the work was arranged by the Colonial Office. The second was in Singapore at a time when the island was crowded by immigrants during the first three months of 1946; this epidemic was investigated by Dr. McFarlan,

whose services were made available to the Supreme Allied Command, South-east Asia, by the Medical Research Council.

The outbreak in St. Helena began in November 1945, and reached its peak in the following month. Apart from a probable epidemic in 1836, which is mentioned in the writings of Sir Charles Bell, the island had previously been free from outbreaks of this disease. In the present epidemic the attack-rate, computed on paralytic cases, was 19 per 1,000; the incidence was highest in the age-group 5–19, and was surprisingly low below the age of 5 (only 21 out of 217 patients); there were 11 fatalities, representing a death-rate of 14 per cent. of all paralytic cases. It was concluded that visitors from a transport from Durban and Capetown bound for Liverpool were probably the medium of introducing the virus to the susceptible island population (Nissen, 1947).

In the Singapore outbreak there were 137 civilian cases, of which 126 were in children under 10 years of age. The attack-rates were 0·2 per 1,000 total population and 0·5 per 1,000 children under 10. The death-rate was 4·5 per cent. The disease spread centrifugally over the island during the epidemic, and the number of cases weekly rose and fell almost symmetrically over eight weeks. Among British troops stationed in Singapore there were 50 cases during the three months; most of them occurred as singletons in different units, and there were only a few instances of apparent case-to-case spread in units. The attack-rate in British troops was higher (0·3 per 1,000) than in adult natives, and the case fatality-rate was 25 per cent. In one group of units (1,600 persons) the attack-rates per 1,000 were 11·6 in officers and 5·0 in other ranks, 18·2 in women and 5·8 in men. The method of spread both in civilians and troops appeared to be by contact with many carriers of the infection (McFarlan, 1946).

## Publications relating to Chapter 4

### DYSPEPSIA IN THE ARMY

NEWMAN, C. E.—
Contribution to discussion on 'Dyspepsia in the Forces'. *Proc. Roy. Soc. Med.*, 1941, **34**, 417; *Brit. med. J.*, 1941, **i**, 530.

PAYNE, R. T.—
Contribution to discussion on 'Dyspepsia in the Forces'. *Proc. Roy. Soc. Med.*, 1941, **34**, 424; *Brit. med. J.*, 1941, **i**, 531.

PAYNE, R. T. and NEWMAN, C.—
Interim report on dyspepsia in the Army. *Brit. med. J.*, 1940, **ii**, 819.

### TUBERCULOSIS

BROOKS, W. D. W.—
Contribution to discussion on 'The place of miniature radiography in the diagnosis of diseases of the chest'. *Proc. Roy. Soc. Med.*, 1943, **36**, 155.
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# CHAPTER 5

# NUTRITION AND MALNUTRITION

In the First World War, dislocation of the food supply of the United Kingdom as a result of the heavy destruction of shipping by enemy action had been a cause of grave anxiety; so much so that at times it seemed doubtful whether the nation would be able to survive this peril. It was natural, therefore, that nutritional problems should occupy a prominent position among the subjects designated for intensive study when hostilities again broke out in 1939. Fortunately a great store of fundamental knowledge of the physiology of nutrition had been accumulated between the wars, very largely as the result of researches by British workers. A major part of the task of Government in planning the nation's war-time larder consisted in ensuring the application of this knowledge to the best advantage in relation to the limited supplies of food available under conditions of blockade. The close co-operation maintained throughout the war between the Medical Research Council, the Ministry of Health, the Ministry of Food and other official and non-official bodies in regard not only to the optimum utilisation of existing knowledge of human nutrition, but also to the arrangement of *ad hoc* studies of feeding problems arising from the war, and the periodical assessment of the nutritional state of the population, was an important factor in safeguarding the situation.

The Ministry of Food, established by Order in Council in September 1939, was responsible for the detailed planning, administration and implementation of war-time food policy; it had wide executive powers in regard not only to the purchasing, distribution, control and rationing of foods, but also to the education of the public in the optimum use of the foods available. From the first the new Ministry naturally worked in intimate consultation with the Ministry of Health, since the health aspects of food policy were the concern of that Ministry. At the highest level the problems of national food requirements and supply were considered by the Food Policy Committee of the War Cabinet, which in the early part of the war had the help of the Scientific Food Policy Committee, a body of independent experts set up in 1940 under the chairmanship of the President of the Royal Society, as mentioned in Chapter 1. During this Committee's work in 1940–41 it became clear that numerous questions affecting the health of the people were likely to arise in the course of the practical application of a national war-time food policy, and the task of advising the Government and other Government Departments on such questions was made a responsibility of the

Minister of Health. To assist in this, a Standing Committee on Medical and Nutritional Problems arising out of the war was appointed by the Minister in May 1941, under the chairmanship of the Chief Medical Officer; in addition to the representatives of the Health Departments and the Ministry of Food, it included nominees of the Ministries of Education, Agriculture and Fisheries, Labour, Supply, Fuel and Power, and of the Medical Research Council, the Agricultural Research Council and the Department of Scientific and Industrial Research (Food Investigation Board). It dealt with a variety of nutritional problems connected with the national scheme of food rationing, such as the allocation of food concentrates and milk to infants, children, pregnant and nursing women, and workers in industry; it also considered questions relating to the nutritive value of various foods such as bread and flour, margarine, milk and sources of vitamins for the artificial feeding of infants. On many of these matters it in turn had the advice of expert committees of the Medical Research Council, including the Accessory Food Factors Committee and its various sub-committees and the Food Rationing (Special Diets) Advisory Committee, some of whose war-time work is described later in this chapter. Another expert committee in the nutritional field, set up by the Medical Research Council primarily in relation to war-time needs, was the Protein Requirements Committee; this was concerned with promoting research on problems such as the metabolic effects of injury (see Chapter 3); it also played an important part in planning suitable diets for the treatment of starvation among the inhabitants of liberated countries; with its aid the Council were able to accede to an official request from the Netherlands Government for advice and help in dealing with the undernutrition encountered in Holland after the enemy had retreated; they were also able, by sending teams of experts to Germany in the latter part of the war in Europe, to make a significant contribution to the problem of treating the extreme forms of malnutrition seen in enemy concentration camps (see section entitled Studies of Malnutrition below). The composition of the expert committees of the Medical Research Council mentioned above is given in Appendix I.

## The Feeding of a Nation at War

The feeding of the British fighting man so as to ensure his maximum fitness and efficiency naturally received the highest priority in the country's nutrition policy, both in the pre-war period and throughout the war. Various contributions to knowledge of this subject made by Service officers and by members of the staff of the Medical Research Council have been discussed in Chapter 2, and they need not be recapitulated here, though publications resulting from some of the studies are included in the list at the end of this chapter.

### THE APPLICATION OF NUTRITIONAL KNOWLEDGE TO THE PLANNING OF THE NATIONAL DIET IN WAR-TIME

A salutary effect of the special attention to nutritional requirements involved in formulating a national food policy in war-time was the adoption, as a matter of urgent expediency, of a number of dietary improvements which had been recommended earlier by research workers in nutritional science. Outstanding examples were the raising of the extraction rate of flour and its fortification with extra calcium. Before the war, the extraction rate of the white flour eaten by the majority of the people had been such as to include about 70 per cent. of the whole wheat grain. The remaining 30 per cent. was used chiefly for feeding animals but was well known to contain the greater proportion of the B vitamins. The need to save shipping space by reducing the amount of wheat imported led to the introduction of a National flour in which the extraction rate was raised to 85 per cent., and the diet of the people was correspondingly enriched in B vitamins. It had long been maintained by experts in nutrition that the pre-war diet of Great Britain was seriously deficient in calcifying properties. The researches of Mellanby and others, on the effect of phytic acid in cereals in restricting the absorption of calcium, not only demonstrated one of the reasons for this deficiency but pointed to a means of remedying it, which was quickly implemented under the stimulus of war emergency, by the addition of extra calcium to the National flour. A number of *ad hoc* experiments by the Accessory Food Factors Committee preceded these recommendations, and the co-operation of the Research Association of British Flour Millers (later to become the Cereals Research Station of the Ministry of Food) was indispensable in making them practicable. The decision to augment the sources of vitamin D in the diet, and the provision of extra milk for pregnant and nursing women and young children were independent, but complementary, measures of great importance.

Despite the greatly reduced supply of fats and of animal protein, and the inevitable limitation of the variety of foodstuffs to be purchased, leading to some monotony of catering, it can be said with confidence, in retrospect, that the diet of the people of the United Kingdom was not only maintained at an adequate level throughout the war period, but was planned more logically, distributed more equitably between all social classes, and contained a higher proportion of certain health producing constituents than ever before. An indication of the success of the national war-time feeding policy is given by the vital statistics for the period, which show that the health of the nation, so far from deteriorating after the introduction of rationing, was generally maintained and in some respects actually improved. There was no evidence of malnutrition nor any serious

evidence of undernutrition among the population of the United Kingdom as a result of war-time food restrictions.

### AN EXPERIMENTAL STUDY OF RATIONING

Before the national rationing scheme was started in 1940, an important experimental study of rationing was carried out at Cambridge by a team of volunteers led by Dr. (now Professor) R. A. McCance and Dr. E. M. Widdowson. The team, consisting of healthy adults of both sexes and varying ages, undertook to subsist for a period of weeks or months on a very restricted ration scale, suddenly imposed, in order to observe its physiological and psychological effects. The rations of the volunteers were planned to correspond with those which might be expected to be accessible to the civilian population under very severe blockade conditions, and which, in the light of existing knowledge, seemed likely to be the minimum needed to maintain a good level of general fitness and well-being. In many respects—such as in the amounts of meat, fats, sugar and milk taken—the experimental rations were much more restricted than those actually available for the population of this country during the war, the blockade conditions envisaged as possible being considerably worse than those ultimately experienced. In other respects, however, the similarity between the experimental diets and the national rationing scales, subsequently adopted, was striking. The volunteers were allowed unlimited quantities of bread, made of a 92 per cent. extraction flour with calcium carbonate added; potatoes and other vegetables were also unrationed in the experimental diets. The quantities of bread and potatoes consumed by the volunteers in lieu of other food were remarkable, and they obtained a large part of their energy requirements in this way. The same, no doubt, applied in the case of the general public during the war years, since potatoes then were unrationed, though sometimes scarce, and bread rationing, even of moderate degree, was not introduced until after the end of hostilities, when the inherent dangers of the blockade were over. The effects of the experimental rations on the volunteers were assessed by biochemical and physiological tests, as well as in terms of their psychological reactions to the restricted diets. At the end of a test period of some three months, it was found that the four volunteers who had been subjected to the complete experiment were very fit and could carry out satisfactorily, and without undue fatigue, most severe exercise tests, requiring a very high expenditure of energy. The experiment was completed early in 1940, and the results were reported confidentially to the War Cabinet and to the various Government departments which would be concerned with problems of food procurement and of food rationing on a national scale; there is no doubt that they materially influenced policy in these regards. It was decided by the Government that the report on the results should not be published during the war

period, but a full account of the experiment was issued subsequently (McCance and Widdowson, 1946).

### EFFECTS OF RATIONING ON THE HEALTH OF THE NATION

From 1940 onwards, periodical dietary surveys—eventually including as many as 1,000 families a month at different economic levels—were organised by the Ministries of Health and of Food in order to assess the average consumption of different foods per household and the approximate consumption per head. A number of more detailed surveys was also made, in which the food eaten was weighed and measured, and in addition the diet of many individuals was estimated. The figures were worked out in terms of nutrients, and showed the amount of calories, protein, calcium, iron, vitamin A, vitamin $B_1$, riboflavin, nicotinic acid and vitamin C consumed. In general, the consumption of each particular nutrient seldom fell below the standard aimed at, but if it did, steps were taken to remedy the defect on a national scale, either by altering the basic rations authorised or by obtaining greater supplies of some particular unrationed commodity (Ministry of Health, 1946).

A number of clinical surveys also was arranged by the Ministry of Health (*loc. cit.*) to determine the effects of dietetic restrictions upon the people; they were directed at first by an expert lent by the Rockefeller Foundation of New York and subsequently by certain officers of the Colonial Medical Service with special knowledge of deficiency diseases. With the co-operation of medical officers of health, the investigators were able to examine many hundreds of persons each week, and to look for clinical signs which might indicate a deficiency of some particular nutrient. In parallel with these studies, the Oxford Nutrition Survey, attached to the biochemical department of the University, carried out more detailed investigations, including the examination of specimens of blood and urine. Further information was obtained through the agency of a committee of the Nutrition Society, which was founded in 1941 to correlate the results of the various surveys. A controlled test was made of the effect of administering a composite supplement of synthetic vitamins to some 2,500 school-children and adults who were in receipt of what might be considered a normal diet. There was no resultant improvement in growth or in physical or mental ability after a year of this treatment, from which it was inferred that no advantage could accrue from such a measure unless the original diet was deficient in vitamins.

A study of the heights and weights of 12,000 children, carried out annually from 1940 onwards, showed that growth rates were well maintained throughout the war period. A body weight survey of adults, undertaken in 1944 and 1945, indicated that there had been no noticeable change, and that up to middle age average weight had continued to increase at the normal rate, although above middle age there was a

slight reduction. Surveys of the state of the teeth of 5-year-old London County Council schoolchildren in 1943 and again in 1945 showed a considerable lessening in the incidence of dental decay compared with findings recorded in a similar survey undertaken in 1929, the figures for 1945 being significantly better than those for 1943.

As a further check on the nutritional state of the population in the fourth year of the war, an investigation of the haemoglobin content of the blood of a very large number of persons was undertaken in 1943 by a special committee of the Medical Research Council at the request of the Ministry of Health; estimations of serum protein levels were also made, but on a very much smaller scale. Haemoglobin estimation was chosen as the main criterion in this inquiry because of its simplicity and because any serious long-continued deficiency of iron or protein is reflected in diminished haemoglobin values, i.e. in anaemia. About 13,000 adults, including 700 pregnant women, and 3,000 children were included in the survey. All observers used the Haldane-Gowers method, as recently standardised by the British Standards Institution. The apparatus used was standardised at the National Physical Laboratory, and the necessary corrections were made in recording the results. Tests were carried out also as to the individual accuracy of the 60 observers who recorded the haemoglobin measurements, and the existence of personal variations was taken into account in the interpretation of the results.

The figures recorded in this study, taken as a whole, showed higher haemoglobin levels than those obtained in a more limited survey carried out in Aberdeen in 1935, but the difference was attributed in part to the fact that the latter figures were largely from individuals who were unemployed or who were in the lowest income groups. It seemed possible that the higher iron content of national bread had resulted in an increased absorption of iron, though the committee were not prepared to make a definite statement on this point. It was concluded that the general situation revealed by the survey was reasonably good, although an effort was still needed to reduce the considerable proportion of low values for haemoglobin observed in certain groups particularly young children, pregnant women, and persons at the lower economic levels (Medical Research Council, 1945). From the long-term point of view an important result of this survey was that it showed up the defects of current methods of haemoglobin estimation and paved the way for improved techniques of haemoglobinometry which have since been devised (see Chapter 9).

An investigation, begun in 1941, with assistance from the Ministry of Health, to determine the effect of war-time dietary changes on the composition of human milk showed that it was always possible for an intelligent mother to obtain a diet which was fully satisfactory in this respect. The findings of the study, which was completed after the war

ended, constitute the most comprehensive account yet published of average values for the constituents of human milk (Kon, Mawson *et al.*, 1950).

For a fuller account of national war-time feeding policy and of some of the surveys made to assess the nutritional state of the population, reference may be made to Civilian Health and Medical Services, Volume I, Chapter 5.

### SPECIAL DIETS FOR INVALIDS AND OTHERS

Early in 1940, an expert committee known as the Food Rationing (Special Diets) Advisory Committee (Appendix I) was set up by the Medical Research Council at the request of the Ministry of Food, the Ministry of Health and the Department of Health for Scotland, to advise on modifications of the ordinary civilian rations which might be necessary on medical grounds for invalids or other persons on special diets. At every meeting, the Ministry of Food was represented by observers, but the committee was a purely advisory body, free to comment on policy, and was independent of the executive; it was thus able to serve as a court of appeal, and to give opinions, generally accepted as disinterested, on the merits of individual applications for special rations. Although, apart from a few *ad hoc* studies, it was not concerned with promoting research, its work was of so much practical importance in relation to the war-time and post-war rationing schemes as to merit a relatively full description here.*

At each meeting, the committee received from the Ministry of Food an estimate of the position regarding food supplies during the next quarter and a statement of any proposed change in rations. On this basis it advised what amendments were necessary to the existing regulations governing rations for invalids, and forecast what further categories of patients would have to be specially provided for in consequence of any new restrictions. Individual cases were considered by the full committee only in as far as they created precedents or raised new issues. The task of dealing with the daily inflow of individual applications was delegated to particular members, who applied and interpreted the rulings of the main body.

The production of a medical certificate was required in all cases of application for extra rations on the grounds of illness, and confidential circulars were sent to all medical practitioners informing them of the conditions which qualified for extra rations.

Cases covered by existing rulings based on the committee's advice were mostly dealt with by the local food offices, the officers simply issuing the authority to purchase the rations against a medical certificate

* A more detailed account of this committee's war-time activities is given in the Report of the Medical Research Council for 1939–45.

giving either the diagnosis or a corresponding code number. Applications claimed to merit special consideration or to raise new issues were dealt with centrally on their merits, specialist advice being sought where necessary. The body of rulings which accumulated from the decisions on individual cases came to play an important part in the system of rationing. They served to amplify more general advice given by the committee, and formed the main basis of the detailed schedule of illnesses provided for the food executive officers in order that they might deal with local inquiries from patients and doctors.

Besides recommending special rations for particular types of invalid, the committee gave advice on certain broader medical aspects of food policy, for example the granting of licences for the importation of natural foods, such as citrus fruits, or of prepared invalid foods not manufactured in Great Britain. With the advent of milk rationing, the whole question of the value of dietary measures in the prevention of industrial disease was raised. Later, when supplies of certain essential foods were at a critically low level, the committee scrutinised every new measure affecting the normal consumer, to judge whether it threatened to augment the already considerable number of persons whose activity was impaired by ill-health. The distribution of soap being a concern of the Ministry of Food, the task of advising on the allocation of extra supplies to invalids and others was also entrusted to the committee.

In the framing of recommendations for the grant of extra food rations to invalids, three principles were adopted; first, that illnesses qualifying for extra rations should be precisely defined, and the concession strictly limited to that particular group of patients; second, that extra rations should be granted only on grounds of proven therapeutic necessity; third, that when it was impossible to satisfy all of several competing claims, priority should be granted to those groups with the better prospect of recovery, or which, by means of special rations, could be kept at work in full vigour. In applying the first of these principles, every effort was made to avoid the use of vague or too inclusive terms. Occasionally, however, the definitions had to be descriptive, as when the type of nephritis for which extra meat was made available was described as 'nephritis with gross albuminuria and oedema', thus avoiding the use of the controversial terms 'nephrosis' or 'nephrotic stage of glomerulo-nephritis'. On other occasions the qualifying condition was a symptom, not a disease, as in the case of spontaneous hypoglycaemia, steatorrhoea and hypoproteinaemia. Generalisations of any kind were avoided, and claims for extra rations on such broad grounds as debility, malnutrition or convalescence were not admitted. Such strictness of definition protected the doctor from undue pressure to grant a certificate, by allowing the onus of refusal to be placed on the Ministry of Food. The relatively few protests

received from the medical profession, and the comparatively small number of requests for special consideration, were indications that the conditions were widely accepted as fair and reasonable. The principle that extra rations should be granted only on grounds of therapeutic necessity excluded applications made mainly on the grounds of the rarity of the particular illness, and led to the rejection of applications in cases where satisfactory alternatives to dietary therapy were available. Similarly, extra rations were not allowed for the construction of those traditional dietaries for invalids and convalescents which, however comforting to the patient, are without known effect on the outcome of the disease.

The third principle, that, in deciding between competing claims, preference should be given to those invalids with better prospects of recovery, or who required special rations to maintain active health and thus be able to contribute to the national effort, guided the committee in one of its most painful and difficult tasks. In the early stages of rationing, it was necessary only to advise whether or not a particular claim for special allowance was justifiable. Later, when food supplies were more restricted, the claims for different groups of invalids had to be considered in relation to one another. Eventually, food supplies became so curtailed that the requirements for invalids had to be weighed against the needs of the general population. It was in the autumn of 1941 that the full implication of the third principle was first enunciated. At that time, about 50 per cent. of the milk available to the whole population was being distributed to persons with priority claims of one kind or another; the individual consumption of animal protein from sources other than milk was under 30 g. a day; the military situation was grave, and the country had need of every able-bodied worker. After careful consideration, the committee advised the Ministry of Food that until the supply of milk was sufficient to provide a full allowance daily to the working population, it would be against the national interest to allow extra milk to mental defectives and hopeless invalids at the expense of the already restricted supplies to active workers. The continued limitation of the food supplies subsequently compelled the committee to extend this advice to cover all rationed foods. It thus came about that mental and physical defectives, the insane, hopeless invalids and the elderly were denied any special food concessions unless, coincidentally, they were suffering from some other condition which itself qualified for extra rations. The only exception to this grim and distasteful ruling was an extra allowance of tea to the elderly, a decision taken by the Ministry of Food on non-medical grounds.

### SPECIAL PROBLEMS

*Diabetes Mellitus.* Extra protein and fat being necessary to compensate for the restriction of carbohydrate intake in diabetes mellitus, patients

with this disease were entitled to obtain two extra fat rations, two extra meat rations and a special allowance of 12 oz. of cheese weekly, and a priority allowance of one pint of liquid milk daily, all in exchange for their sugar ration. Vegetarian diabetics were allowed to take their fat ration in the form of margarine made from vegetable oils, and the normal allowance of butter; in the place of the normal bacon ration, they were allowed 24 oz. of cheese weekly. The generous allowance of fat was provided to meet the needs of those diabetics who, by greatly restricting their intake of carbohydrates and substituting fat, can avoid, or restrict, the use of insulin. Extra sugar was available only to diabetics in ketosis, when two rations could be obtained at once in exchange for the fat ration.

'*Spontaneous*' *Hypoglycaemia.* The committee insisted on biochemical proof of the diagnosis of this condition, a blood sugar value below 60 mg. per 100 ml. being accepted for the purpose. The rations made available to proven cases were either those provided for diabetic patients, or two extra rations of cane sugar weekly, according to the method of treatment favoured by the doctor.

*Steatorrhoea.* Under this heading were included conditions such as coeliac disease, idiopathic steatorrhoea and sprue, all of which are characterised in their active phases by an excessive excretion of fat in the stools. For the acute stage, four extra meat rations and two tins of skim milk powder were allowed weekly in place of the normal fat ration. For the convalescent stage, one extra meat ration and two tins of skim milk powder were allowed weekly, but cancellation of the normal fat ration was not required. Later, dried bananas became available, and were granted to active cases of steatorrhoea as a variation on the restricted diets otherwise available. As soon as it was announced that extra rations of meat were available for cases of steatorrhoea, applications began to arrive in numbers out of all proportion to the general experience of the frequency of the condition. It was therefore found necessary to insist that particulars of the fat content of the stools should accompany any request for extra rations on the ground of steatorrhoea, an excretion of 25 per cent. or more of fat in the dry weight of the stool when the patient was on a normal diet, or proportionately less when the intake of fat was restricted, being accepted as establishing its presence.

*Anaemias.* Two main forms of anaemia were the subject of applications, iron-deficiency anaemia and pernicious anaemia. No extra rations were allowed for the former, since it was considered that such cases could be adequately treated by preparations of iron. The applications in respect of pernicious anaemia were from patients under treatment with fresh liver. In the majority of cases the application was refused, since treatment with fresh liver was known to be less efficient than parenteral injection of the extract. A minority of applications was based

on supposed sensitivity to injected liver extracts, and to proven cases of this nature fresh liver in amounts equivalent to two extra meat rations weekly was allowed. The concession was made because the procedure of desensitisation was so exacting that it might be impracticable for a busy doctor.

*Tuberculosis.* At the outbreak of war investigations were in train at the Mundesley Sanatorium to determine the effect of an increased intake of carbohydrate in tuberculosis. A second investigation, on the effect in such cases of a comparable consumption of fat, was set on foot by the committee at Tor-na-Dee Sanatorium, and the results of both researches became available just as rationing began to be severe. They showed that fat had no advantage over carbohydrate, and further that, after two or three months on a high fat diet, the appetites of tuberculous patients declined and their weights fell, effects which did not occur on a high carbohydrate diet. Since carbohydrate was available in ample quantities, no increase in the fat ration was granted. Reports subsequently received from various sanatoria and municipal authorities gave no indication of a deterioration of the condition of tuberculous patients as a result of this decision. The committee's view that the rations available for tuberculous patients were adequate was endorsed by the Tuberculosis Association and the Joint Tuberculosis Council; the only special rations allowed were two pints of liquid milk daily for cases of active tuberculosis, and later, when the cooking fat ration was reduced, the supplies to tuberculous patients were continued at the previous level.

*Burns, Chronic Suppuration, and Liver Diseases.* Many investigations were carried out in Great Britain and elsewhere during the war on the effect of a high protein diet in these conditions. Though the desirability of recommending special allowances of meat for such cases was realised, the supply situation did not permit it; the most that could be done was to allow two tins of skim milk powder to patients with hepatitis, and to express the hope that cases of burns and chronic suppuration would receive extra rations from the bloc allocations and spread-over of rations to hospitals. Later, extra rations were allowed for certain cases of liver disease.

*Food Sensitivity.* As soon as it was announced that butter was to be rationed, the Ministry of Food received a large number of applications for extra butter, based on alleged sensitivity to margarine. The committee advised the Ministry that such requests should be granted only in cases where specified tests demonstrated genuine sensitivity, an essential part of the test being that the patient should correctly distinguish margarine from butter where the taste was disguised. As soon as this requirement became known the number of such applications declined abruptly, and among the small number of persons who underwent the tests no clear instance of margarine sensitivity was obtained. Similar complaints of sensitivity coincided with, or in some cases

actually anticipated, changes in the type of flour. Extracts of the new flour were prepared and tested on persons known to be sensitive to different kinds of food, but little support was found for the view that a person could be sensitive to National flour and insensitive to white flour. There was, however, ample evidence that persons giving positive skin tests to either flour might eat bread made from it with impunity. Tests were made also with the various diluents, such as rye, barley, oat or potato flour, which might need to be added to wheaten flour to eke out limited supplies. Generally speaking, a much smaller proportion of persons reacted to these than to wheat, both among the ordinary population and those already known to be sensitive to wheaten flour. The procedure adopted to deal with cases of alleged sensitivity to any form of wheaten flour was to offer the subjects rye flour, or, if they still insisted on claiming white flour, to provide their medical attendant with extracts made from National flour and ask him to test their skin sensitivity to it in comparison with an extract of white flour. Only one subject was reported as reacting to the former and not to the latter. Applicants adducing reasonable evidence of sensitivity to any of the flours used on occasion to dilute wheaten flour were provided with pure wheat flour.

Throughout the war period a small but steady stream of applications was received for special supplies of condensed milk because of alleged sensitivity to raw cow's milk. In such cases the applicants' medical attendants were advised to order the milk to be boiled; and judging by the small number of renewed requests, this measure usually sufficed. The general conclusion of the committee in regard to food sensitivity was that many cases were more imaginary than real; it is not thereby implied that the applications were fraudulent or that the applicants had no symptoms, but the influence of psychological factors in such cases is well known and their importance was emphasised by the committee's experience.

*Industrial Hazards and Diseases.* Despite the widespread popular belief in the protective value of milk against certain poisons, there was no statutory obligation upon employers in the United Kingdom to supply milk to workers in any trade, the only legal enactment to supply food to employees while at work being contained in the pottery regulations; it related only to women and young persons employed in processes of long duration, and made no specific mention of a need to give milk even to users of lead glaze; in practice, however, milk was generally provided, because it was the most convenient food. All other undertakings to supply milk were in the nature of agreements between employers and employees, or voluntary grants of an amenity; in the former type of arrangement the provision of milk is based on the belief that it militates against a particular industrial risk, and the undertaking is formally incorporated in what are known as 'trade rules'. Few of such agreements had a sound toxicological basis. It was obviously impossible,

however, to reinvestigate the whole problem of the dietary prophylaxis of industrial disease, and the committee agreed to accept established practice when this appeared to be founded on reasonable supposition. Thus milk for consumption while on duty was granted to workers with lead and to those working with nitro or amino derivatives of benzene or toluene. The last group was of particular importance because it included workers with trinitrotoluene (T.N.T.). The opinion that milk protected against the toxic effects of this explosive had gained credence during the War of 1914–18. Accordingly, extra milk was at first allowed, but later it was discovered that, although protein appeared to reduce the toxicity of T.N.T., fat increased it. The Ministry of Food was therefore advised to replace the milk with a drink made from defatted cocoa, skim milk powder and saccharine.

*Pregnant or Nursing Women, and Infants.* Expectant mothers were allowed to obtain, in addition to their own rations of protein foods and vitamins, the corresponding foods allowed on a child's ration book; the nursing mother was similarly allowed the benefit of her child's rations. The chief problem arose in relation to milk, due to the different methods of infant feeding. Normally mother and child together received 14 pints of liquid cow's milk weekly, 7 pints being in the mother's right and 7 in the child's; if the child was fed entirely at the breast, the mother thus obtained 2 pints of milk daily. If cow's milk only was used, a further 2½ pints weekly was obtainable on request. Full and half-cream national dried milk were also available, and infants fed on these received amounts appropriate to their age, instead of the normal allowance of liquid milk. Special provision, in the form of extra cow's milk, was made for mothers using supplementary feeds of dried milk while striving to increase their supply of breast milk. Evaporated (condensed) milk was not normally issued, and when 'points' from the ration card had to be surrendered to get it, applications for special supplies were received. Such milk was made available only for infants under the age of 12 months; for them it was obtainable immediately for a period of one month, on receipt of the necessary medical certificate. Supplies were thus ensured to premature infants.

*Problems of Milk Rationing.* It was agreed that priority claims on the supply of liquid milk should be limited to patients for whom a liberal intake of milk was an indispensable part of medical treatment. The scheme ultimately adopted was to divide the qualifying illnesses into categories and groups of relative priority, and, to ensure economy, the allowance of milk was adjusted to need, the assessment of which was necessarily left in the hands of the medical profession. Thus, cases of peptic ulcer received 2 pints daily, cases of dyspepsia not certainly due to peptic ulceration, 1 pint. For every three certificates relating to the former condition there were two relating to the latter. If the latter category had not been provided, and if the medical profession had not

co-operated in using it, the majority of the applicants given certificates would have been included in the group receiving 2 pints of milk daily, thereby greatly increasing the total milk consumption and constituting a serious and unjustifiable drain on the limited supplies. Despite the personal pressure to which medical practitioners must often have been exposed, they continued in general to exercise scrupulous care in giving certificates, as was shown by the constancy of the milk consumption by invalids throughout the period of hostilities when food shortage was becoming increasingly more severe.

*Problems concerning the National Flour.* Besides the allegations of 'food sensitivity' already noted, the introduction of National flour elicited protests for two other reasons—its supposed irritant effect on the gastro-intestinal tract, and the supposed baneful effect of the calcium salt with which it was fortified.

Complaints of irritative properties in the new flour came mainly from patients with colitis, especially mucous colitis. Before the flour was introduced, however, the committee had arranged clinical tests which showed that it was well tolerated in all types of colitis, and could be taken with impunity also by patients with peptic ulceration. Complaints of similar kinds were received from patients with colostomies, many of them based on the erroneous assumption that the new flour had a high roughage content. The roughage content was, in truth, but little greater than that of white flour, but when National flour was first introduced it contained bran particles which were coarse and visible. Their removal with a flour dredger was advised, and judging by the absence of renewed appeals the procedure was satisfactory. A special problem arose in connexion with certain infant foods which contained a considerable proportion of wheaten flour; the manufacturers claimed that National flour could not be used, because it would cause diarrhoea. Comparative tests carried out in three children's hospitals gave no support to this allegation, and the committee accordingly advised the Ministry of Food to stop the special allowance of white flour to the manufacturers of cereal-containing infant foods. No complaints were subsequently received of any untoward effects from the new preparation.

The proposal to add calcium carbonate to the National flour evoked another storm of protest. Divers ill-effects ranging from arteriosclerosis to nephrolithiasis were anticipated. Actually, the amount of calcium added to the flour was hardly more than that needed to compensate for the amount of phytic acid it contained. The committee, therefore, had no hesitation in advising the Ministry of Food that the addition of the proposed amount of calcium to bread would be harmless to invalids.

## THE SCIENTIFIC HARVEST OF THE COMMITTEE'S WORK

During the years of rationing a great volume of information relating to dietetics was accumulated. Valuable data resulted from the investigations

into the sensitivity of individuals to cereals, the tolerance of infants for high extraction flour, the use of bananas in the treatment of steatorrhoea, the nitrogen balance of giants, and other *ad hoc* inquiries which the committee had promoted in relation to its work. Useful knowledge was acquired also about the effect of different diets on the course of pulmonary tuberculosis and other diseases. In administering the regulations concerning special rations for invalids, the Ministry of Food amassed a vast quantity of statistical data relating to the incidence and distribution of different diseases in Great Britain; most of these diseases were not notifiable and their incidence could hitherto only be conjectured from the mortality rates. There is good reason to believe that many of the morbidity figures acquired in relation to the food rationing scheme correspond closely with the true incidence, and by their use it may thus be possible for the first time to estimate, with some approach to accuracy, the general and local distributions in the country of conditions such as diabetes mellitus, steatorrhoea, thyrotoxicosis, nephritis, spontaneous hypoglycaemia, and peptic ulcer, and perhaps even to establish a correlation between these and the corresponding mortality rates.

## RESEARCHES UNDER THE ACCESSORY FOOD FACTORS COMMITTEE ON VITAMIN A AND VITAMIN C

*Vitamin A.* At the outbreak of war, preparations were in train for a meeting of the International Conference on Vitamin Standards. The value for the conversion factor for relating the results of spectrophotometric tests for vitamin A content with the results of biological tests had been widely discussed ever since the second International Conference on Vitamin Standards in 1934 had fixed the figure provisionally at 1,600. Between 1935 and 1940 the Vitamin A Sub-Committee of the Accessory Food Factors Committee of the Medical Research Council had organised trials to determine the value of this factor for several different preparations of fish liver oils. The work was completed in 1942, and from the pooled results of the tests a figure of 1,740 was recommended for the conversion factor (Vitamin A Sub-Committee of the Accessory Food Factors Committee, 1943).

In July 1941, it appeared that the vitamin A potency of the vitaminised margarine then being issued as an essential part of the national ration was below the scheduled value of 20 i.u. per g. Routine spectrophotometric tests showed a loss of potency of 25 to 30 per cent. when vitamin A was added in the free form as the alcohol, and of 10 per cent. when it was in the combined form as the ester. Biological tests, made on the same material as the spectrophotometric tests, were necessary to determine whether or not the loss was real. A series of such tests was therefore planned by the Vitamin A Sub-Committee, to be made in five laboratories, with margarines containing vitamin A in the one

form or the other and, for purposes of comparison, with butter and a 'dummy' butter; the last was prepared from a fat blend as used for margarine, with the addition of vitamin A concentrate and pure β-carotene in the proportions found in the average summer butter. The results showed that both types of margarine, and the dummy butter, had a vitamin potency of from 12 to 20 per cent. less than that expected. It was found also that with margarine containing the ester of vitamin A there was no subsequent decline of vitamin-A potency, but with the margarine containing the alcohol the potency fell to 60 per cent. of the scheduled value within six months.

In view of the world shortage of vitamin A, and the conflicting reports as to the minimum amount necessary to maintain health, the Ministry of Food in 1942 sought information from the Medical Research Council about the vitamin-A or carotene requirements of human adults. It was evident that the question could be settled satisfactorily only by an experiment in man, and this was carried out at the Sorby Research Institute, Sheffield, from July 1942 till October 1944. A group of twenty-three conscientious objectors volunteered to live on a diet as deficient as possible in vitamin A and carotene, but complete in all other respects. The diet, which consisted of natural foodstuffs, contained no vitamin A as such, and only about 70 i.u. per head daily of carotene. Seven of the volunteers received this deficient diet with daily supplements of 2,500 i.u. of vitamin A, or about 5,000 i.u. of carotene in oil or margarine, carrots, spinach or cabbage; the remaining sixteen received the diet unsupplemented. Carotene was estimated for set periods in the faeces of those receiving the carotene supplements, so that the amount retained from the various sources could be determined.

The research was planned with three chief objects: (i) to observe the early signs of deprivation of vitamin A, about which there had been much dispute; (ii) to determine the amount of the adult human requirement in terms of vitamin A; and (iii) to determine the amount of the adult human requirement in terms of carotene.

Of the sixteen individuals subjected to deprivation, none showed any signs of deficiency of vitamin A within a year. After 14, 17 and 22 months respectively, three showed the effects described below. The remainder continued to receive the deficient diet for periods of up to two years without showing any sign of depletion other than a slow fall in the blood plasma content of vitamin A; one, after twenty-two and a half months' deprivation, did not show even this. In the three depleted subjects who showed evidence of deficiency, there was a marked fall in the plasma content of vitamin A, and a deterioration of the capacity for dark adaptation. No changes in the sclera or cornea were observed with the slit lamp. Follicular hyperkeratosis occurred, but it was not specifically related to the state of vitamin A nutrition. No thrombopenia was detected.

The evidence from this experiment, and the results of a contemporaneous survey of the liver reserves of vitamin A in persons dying from accident in Great Britain, were consistent with a value of 1,300 i.u. daily for the minimum protective dose of vitamin A for adults. To provide for the inherent variations found in normal adults, and for differences in activity and environment, an intake of about twice this dose, or 2,500 i.u. daily, was recommended.

On the supposition that 100 per cent. of the carotene ingested is available, the minimum protective dose of β-carotene was assessed as 1,500 i.u. daily, and the figure of 3,000 i.u. daily was put forward as the amount required to cover individual variations and to leave a margin of safety. Carotene, however, is badly absorbed, and is never available to the extent of 100 per cent. from any known source, so that the basal factor of 3,000 i.u. daily must be augmented by another factor appropriate to the individual food in which the carotene is supplied. The factors obtained in this investigation were: for carrots, boiled, sliced or puree, 4; for canned homogenised carrots, 1·8; for cabbage and spinach, 2·5; and for β-carotene in fat, 1·3. The difficulty of fixing any one general figure for the daily requirement of carotene was therefore obvious, but the value of 7,500 i.u. (three times that recommended for vitamin A) was suggested as a figure roughly representative of the proportions in which the different sources of carotene occur in the whole diet (Medical Research Council, 1945, 1949).

*Vitamin C* (*Ascorbic Acid*). During the war years there was a considerable increase in the consumption of vitamin C, partly because of its somewhat indiscriminate use by surgeons as a routine measure for accelerating wound healing, and partly because ascorbic acid was taken by many healthy persons as a supposedly useful supplement to their rations. Since the supplies of ascorbic acid available at that time were limited, it was important to establish with accuracy the human requirement of the vitamin. Previous estimations by authoritative bodies were widely divergent; for example, the Technical Commission of the League of Nations in 1937 had proposed 30 mg. ascorbic acid daily as the adult requirement, whereas the Committee on Food and Nutrition of the National Research Council, U.S.A., had recommended 70–75 mg. daily. An explanation was needed also for the frequent records in nutritional surveys carried out in Great Britain of blood ascorbic acid levels as low as 0·2 mg. per 100 ml., i.e. about one-fifth of normal. These low levels were not associated with any symptoms of vitamin-C deficiency, and it was not known whether they had any significance for health.

It was therefore decided to undertake a critical investigation of the human requirement of vitamin C, and with this aim in view the existing Vitamin C Sub-committee of the Accessory Food Factors Committee was reorganised and enlarged. The investigation was carried out at the

Sorby Research Institute, Sheffield, and began in October 1944. Most of the subjects were conscientious objectors and some of them had taken part in the vitamin A experiment mentioned above. They were divided into three groups: one, of three men, receiving 70 mg. ascorbic acid daily; another, of seven men receiving 10 mg. daily; and a third, of nine men and one woman, receiving no vitamin C beyond the small amount (about 1 mg. daily) present in the basal diet.

The first sign of deficiency in those virtually deprived of the vitamin was an appearance of the skin resembling goose flesh and associated with haemorrhages into the hair follicles, which was noted after 190 to 240 days. Acne, which was present in several members of the deprived group at the beginning of the trial, increased in extent and severity, and the lesions later became haemorrhagic. The blood ascorbic acid values had by then fallen to 0·05 mg. per 100 ml. plasma and to less than 1 mg. per 100 g. white blood cells. During the succeeding weeks the skin condition deteriorated and in all but one member of the group haemorrhages into the gums appeared. One subject, who had previously felt no disability, was taken ill, sixteen hours after a severe agility test, with a pain diagnosed as probably due to pericardial or myocardial haemorrhage; he recovered within a few hours after receiving 7 g. of ascorbic acid. A second subject was found to be suffering from heart-block and was similarly treated with success. In both cases the treatment led to a dramatic improvement in the skin condition and in general well-being. When their condition had been definitely diagnosed as scurvy, six of the deprived subjects were given a dose of 10 mg. ascorbic acid daily. As a result of this treatment they showed a fairly rapid improvement; the dose was later raised to 20 mg. daily without much additional effect. None of the ten subjects who received 10 mg. or more of ascorbic acid daily showed any signs of scurvy, and no definite skin changes were seen in those who received 10 mg. daily for fourteen months.

It was hoped that the values obtained for the vitamin-C content of the plasma and white cells in the groups receiving the various supplements might provide a basis on which to assess nutritional status in respect of vitamin C in the community at large. The vitamin-C content of the plasma with an intake of 70 mg. daily was about 0·55 mg. per 100 ml. A still larger daily intake was necessary to reach higher values. For the deprived volunteers the average value ranged from 0 to about 0·03 mg. per 100 ml., and for those receiving 10 mg. daily the range was little greater, being from 0·01 to 0·05 mg. per 100 ml. Values of from 0 to 0·03 were thus associated with scurvy, and values of from 0·01 to 0·05 were not. No method of estimating vitamin C was able to distinguish reliably between values below 0·05 mg. per 100 ml., so that it obviously would not be possible to use the plasma values as a basis for assessing nutritional status at the critically low intakes. The white

cells in the blood contain a considerably greater concentration of vitamin C than the plasma; in the subjects receiving 70 mg. daily it averaged 16·6 mg. per 100 g.; in the deprived subjects it fell to below 1 mg., and in those receiving 10 mg. daily it was about 1 mg. higher. The white-cell content of ascorbic acid accordingly seemed more likely than the plasma content to provide a measure of nutritional status in respect of vitamin C.

The investigation provided an opportunity to study also the influence of vitamin-C deficiency on the healing of experimentally produced wounds in man. The standard wounds included small incisions and stab wounds on the thighs of the volunteers. When the wounds were excised for examination ten days after infliction, no differences were revealed between the subjects of the three groups, in regard to the tensile strength or histological appearance of the tissues in the zone of wound healing. When, however, the wound tissue was excised twenty-one days after infliction, that from subjects in the deprived group showed a lower tensile strength and less collagen than wound tissue taken from subjects receiving 10 mg. or 70 mg. daily. In the two last groups, healing of the wounds appeared to proceed satisfactorily.

In the group deprived of vitamin C there was no evidence of anaemia or of changes in pulse-rate, temperature or body weight. In the deprived subjects the behaviour of the scars left after the experimental wounds had been excised was in accordance with the descriptions given in the accounts of voyages made when the aetiology of scurvy was still unknown.

The conclusion reached as the result of the whole study was that in the group under test, which consisted of normal young adults leading a life without strenuous physical work, the minimum protective dose of vitamin C was in the region of 10 mg. daily. Tests of physical fatigue, however, left some slight doubt whether 10 mg. was the optimum dose, since the statistical analysis revealed small differences in favour of the group receiving 70 mg. against that receiving 10 mg. It was decided that, in order to provide for individual variations and circumstances and to allow a margin of safety, the minimum protective dose might well be trebled, thus conforming with the figure of 30 mg. daily proposed by the League of Nations Technical Commission on Nutrition. The fact that the period of deprivation needed to produce signs of scurvy or of any deterioration was as long as six months, suggests that even if intakes below 10 mg. daily are liable to occur among the general population in winter, they cannot be continued for long enough to have a detrimental effect (Medical Research Council, 1948).

## Studies of Malnutrition

It has already been mentioned that no evidence of any serious malnutrition or undernutrition among the people in Great Britain came

to light during the war years, in spite of the close watch for any such manifestations which was maintained by the Government Departments concerned. In certain other countries, however, more especially in the Far East, severe malnutrition was by no means uncommon. The condition arose for the most part from dearth of available food, as in the Bengal famine of 1944, or from deliberate starvation or underfeeding of men and women confined in enemy prison and concentration camps.

## MALNUTRITION IN PRISONERS-OF-WAR, INTERNEES AND CIVIL POPULATIONS

For obvious reasons the conditions in prison camps were unsuited to any elaborate kind of medical research. Nevertheless, a surprising amount of good work was done, often under conditions of appalling difficulty, by medical officers who were themselves prisoners, and valuable clinical observations were made on many different aspects of malnutrition. Towards the end of the war the liberation of occupied territories and the release of prisoners—both in Europe and the Far East—opened the way for more extensive investigations by special relief and research teams, which included both clinical and laboratory studies. However, the treatment of survivors among the malnourished was fortunately achieved so rapidly that prolonged investigations were usually ruled out.

The results of three types of inquiry will be briefly surveyed here: (*a*) clinical observations on deficiency diseases among prisoners, mainly in the Far East; (*b*) clinical and biochemical investigations of hunger oedema; (*c*) clinical trials of methods of treating the severely undernourished.

### DEFICIENCY DISEASES

Clinical manifestations of deficiencies of the B vitamins were studied in British prisoners throughout the Far East, including Singapore, Hong Kong and the camps in Formosa, Manchuria and Japan proper. An account of the observations made in the military camp at Singapore and in civilian camps at Hong Kong and Singapore has been published in a Special Report of the Medical Research Council by Smith and Woodruff (1951).

Deficiency symptoms were less common among civilian internees than among military prisoners (Williams, 1946), and rarer in the camps of Japan and Manchuria than in Singapore and Hong Kong (Bennet, 1946). Beriberi was the commonest deficiency disease to be recognised; its comparative rarity in Japan was due to the usual practice there of issuing unpolished rice far more often than polished rice. Burgess (1946) was able to forecast the appearance of beriberi in the military camp at Singapore from calculations of the amount of vitamin $B_1$ in the diet; beriberi occurred only when the daily intake of the vitamin

was less than 0·3 mg. per 1,000 non-fat calories. In Hong Kong, beriberi was first seen in the civilian prison camp three months after the Japanese occupation (Smith, 1946). It could be prevented by giving 3 mg. of crystalline vitamin $B_1$ every other day, but not by giving 10 mg. once a week. Established cases could be cured by a dose of from 5 to 10 mg. given intramuscularly once a day for ten days. Smith found that the number of cases of beriberi increased when the amount of vitamin $B_1$ in the diet fell below 0·42 mg. per 1,000 carbohydrate calories.

Pellagra was by no means rare among prisoners in the Far East; it was not infrequently associated with symptoms of riboflavin deficiency (Smith, 1946). Attempts were made in Singapore to increase the riboflavin content of the diet by giving extracts of rapidly growing shoots of grasses and other plants (Burgess, 1947). A painful complaint known as 'burning feet', 'aching feet' or 'electric feet' was common in both Hong Kong and Singapore (Cruickshank, 1946; Jackson, 1946; Smith, 1946). It seemed clearly to be related to one or more specific dietary deficiencies, but not particularly to beriberi. Many of the cases responded well to nicotinamide (Cruickshank, 1946); Landor (1946) suggested that the improvement might have been due to the drug's vasodilatory effect rather than to its supplying a missing essential nutrient. The most probable deficiency is now thought to have been of pantothenic acid.

Among the symptoms noted in all the prison camps in the Far East were diarrhoea, nocturnal diuresis, oedema, and in women amenorrhoea; these symptoms were not traceable to any single deficiency. Special attention was given to oedema, as described below.

### HUNGER OR FAMINE OEDEMA

A diagnosis of hunger oedema was made in cases showing oedema without obvious renal or cardiac disturbances and with none of the neurological signs of beriberi. Biochemical investigations were not possible in the prison camps during the war, but Cruickshank (1946) estimated the serum proteins of 20 soldiers with oedema at Singapore, immediately after their release, and found a mean figure of 4·72 g. per 100 ml. Allen and Scott-MacGregor (1946) noted that oedema appeared from time to time in otherwise healthy subjects. Giving sodium chloride to such people in excess of their usual needs provoked visible oedema in five out of seven individuals who were subjected to the test. Stapleton (1946) noted the onset of oedema in 98 out of 900 Australian ex-prisoners after a few days or weeks of normal feeding.

*Laboratory Investigations of Oedema.* Many cases of severe emaciation and extensive oedema were found in Holland, and especially in the German concentration camps, when the Western Armies drove forward into Europe in 1945. Teams of relief and research workers had

been organised to study as well as feed the starving populations at the earliest possible moment after liberation, and in this way important scientific investigations were made.

Attention was naturally paid to hunger oedema and its relation to the level of protein in the plasma. In some of the series of cases observed, low plasma protein values were almost always found when visible oedema was present (Denz, 1947; Vaughan, Dent and Pitt-Rivers, 1945; Leyton, 1946). Observers in Holland (various authors, 1948) were impressed, however, with the lack of any very close relation between plasma protein levels and oedema. Patients with oedema had protein levels ranging from 4·6 to 7·78 g. per 100 ml., and the extent of the swelling fluctuated from day to day with no corresponding rise or fall in the level of the plasma protein. Sinclair (1948) also found no relation between the level of serum protein or serum albumin and the occurrence of oedema. Similarly, Mollison (1946) found among the inmates of Belsen camp no clear relation between the protein levels in the plasma and the presence of oedema; all the inmates had low plasma protein values but they did not all show oedema.

Denz (1947) found that hunger oedema tended to disappear with rest in bed and could be made to reappear rapidly by making the subjects do physical exercise. Beattie, Herbert and Bell (1947), as the result of observations they had made on 27 Dutch patients and 11 German civilian prisoners, suggested that hunger oedema might be divided into two categories, one with, and the other without, hypoproteinaemia. Even so, the two types tended to merge into one another, and it was not at all clear what factors other than low protein values helped to determine the onset of oedema. It seems clear, in any event, that the mechanism of hunger oedema is much more complicated than has hitherto been supposed.

### TREATMENT OF THE SEVERELY UNDERNOURISHED

The Bengal famine of 1943 focussed attention on the need to explore methods of treating people who were on the brink of death from starvation (Commission of Enquiry, 1945). It was reported that many of those who were so collapsed that they could swallow nothing, revived quickly after receiving intravenous injections. Protein hydrolysates with glucose and members of the vitamin-B complex seemed to be particularly effective, and after a short period of such injections the subjects were able to take suitable food by mouth.

In the early months of 1945 it became apparent that the liberating armies of the West would shortly overrun territories in which malnutrition would be rife. The Protein Requirements Committee of the Medical Research Council was asked to make plans to deal with the urgent problem of re-feeding such starving people. The committee was impressed with the reports which were just coming through from India

of the value of protein hydrolysates in the treatment of severe malnutrition in Bengal, and the Netherlands Government in London, hearing of the Indian experiences, invited the Medical Research Council to assist in the re-feeding of the Dutch people as soon as possible after their liberation. Members of the committee went to Holland to examine the situation on the spot and came back with a scheme to provide protein hydrolysate for the treatment of 60,000 people. In addition, they planned to send over large stocks of blood plasma, glucose, milk powder and vitamin preparations, the whole to be available for use within six weeks. Medical students were trained to administer the intravenous and oral preparations which were being prepared.

The arrangements were tackled with great energy and completed in the scheduled time. Fortunately, however, the degree of undernutrition met with in Holland when the Germans retreated was not so catastrophic as had been anticipated, though the relief teams following in the wake of the advancing troops found quite enough cases of serious malnutrition to test their available methods of treatment. The admirable work done by these teams has been described in the Report on Malnutrition and Starvation in Western Netherlands (various authors, 1948). The following salient points emerge from this work:

(i) Predigested foods (i.e. protein hydrolysates) are not essential for treating persons in the advanced stages of starvation.

(ii) Digestion of milk and fats can still proceed in the gastro-intestinal tract of even extremely undernourished subjects. It is only when patients are almost dying of starvation that digestion fails, and under such conditions parenteral feeding with protein hydrolysates is unlikely to save them.

(iii) Starving people need abundance of food; they do not have to be nursed back slowly to a state in which they can take a full diet.

While the relief work was proceeding in Holland, concentration camps were being discovered in Germany in which thousands of prisoners were dying from starvation. Some of the relief and research workers who had been destined for service in Holland were diverted to Germany to assist in dealing with the appalling state of affairs which was found in camps such as Belsen. The Medical Research Council sponsored such a team, which included Dr. C. E. Dent, Mrs. R. Pitt-Rivers and Dr. Janet M. Vaughan. In a report (unpublished), submitted to the Council, this team concluded, as did the workers in Holland, that the intravenous protein hydrolysates tested were not of much value for treating starving people under the conditions prevalent in Europe. They were not as a rule well tolerated by very severely malnourished subjects, who could not be given enough to allow them to maintain their nitrogen balance without increasing their fluid intake to a dangerous level. Oral administration of the hydrolysates for any considerable length of time proved impracticable on account of their

unpalatability. Patients who could not swallow improved quickly when they were given intravenous injections of double strength serum. Those who could swallow recovered well on a mixture of glucose and spray-dried separated milk.

Elsewhere in Germany and in the Far East it was found that enormous amounts of food were usually well tolerated by the severely undernourished. Murray (1947), writing of recovery from starvation in Sandbostel camp, says that diets containing 330 g. protein, 350 g. fat and 7,000 to 8,000 calories were eaten without ill-effects. Laycock (1944), who was concerned with the re-feeding of starving Chinese, found the problem rather more difficult. There were two types of patient, which could not be distinguished when treatment was begun. One type showed rapid general improvement and uninterrupted recovery, while the other was subject to relapses and made slow progress; sudden death from no apparent cause was not uncommon in this group.

The general experience, then, was that severely undernourished people needed abundance of calories and protein and that only in the most advanced cases was it impossible to supply these in the form of simple common foods.

## SPECIAL STUDIES IN INDIA

### ANAEMIA IN INDIAN SOLDIERS

Anaemia in the Indian soldier was a major medical problem on the Indo-Burma front during 1943, and General Headquarters, India Command, set up a special team to investigate it. The study took place between September 1943 and January 1945.

'Haemoglobin surveys' were carried out on groups of soldiers, pioneers and recruits. A haemoglobin level of not less than 14 g. per 100 ml. was accepted as satisfactory, and one of less than 11 g. as indicating anaemia severe enough to require hospital treatment. Detailed blood examination in some 600 recruits showed that their anaemias were mostly normocytic and normochromic, less often hypochromic; few instances of macrocytic anaemia were found. In the reports on the study (Army Pathology Advisory Committee, General Headquarters, India, 1945; Hynes, Ishaq and Morris, 1945), possible aetiological factors in the anaemias are discussed in detail: it is concluded that hookworm infestation, though widespread, was probably only a secondary factor. Remarkable benefit was obtained, even in normochromic cases, by giving iron in the form of ferrous sulphate.

### MARASMUS AMONG REPATRIATED INDIAN PRISONERS-OF-WAR

A special unit, known as the Marasmus Research Team, was established by General Headquarters, India Command, in 1945, to investigate this condition among repatriated Indian prisoners-of-war, many of

whom had been in Japanese hands in the Far East for three and a half years. The standard diet issued by the Japanese to Indian prisoners had consisted of 12 oz. of rice and about 8 oz. of green vegetables daily, with a little tea and sugar; this ration was automatically reduced by half if the man was admitted to hospital. In some localities small supplements of meat, fish and red palm oil had been available, and the condition of the prisoners there showed correspondingly less deterioration. Intercurrent diseases, such as dysentery, malaria and helminthiasis, were common.

About 2,000 patients were examined; they could be divided clinically into four main groups: (1) those in whom wasting was the chief feature; these made up about 60 per cent. of the total; they mostly recovered rapidly on a diet rich in calories, proteins and vitamins; (2) those with wasting, severe hypoproteinaemia and oedema, representing about 1 per cent. of the total; though gravely ill on admission, these men generally responded well to transfusions of concentrated plasma; (3) those with wasting accompanied by signs of riboflavin or nicotinic acid deficiency, comprising about 10 per cent. of the total; (4) those with wasting and residual neurological syndromes. The neurological conditions encountered were: peripheral neuritis (beriberi)—about 20 per cent. of the total; a condition described as 'captivity cord syndrome' (degeneration of the long tracts of the spinal cord, leading to ataxia and spasticity)—about 2 per cent. of the total; and 'captivity amblyopia'—about 9 per cent. of the total. A considerable degree of recovery occurred in the cases of ataxia and amblyopia, but the patients with pyramidal-tract involvement had not improved after three months' observation. Haematological investigations revealed anaemia of macrocytic and normochromic type in most of the patients studied. A low serum protein concentration was characteristic, the reduction affecting the albumen fraction only; the serum albumen concentration was correlated more closely than the total protein concentration with the development of oedema. Remarkably low serum calcium values were found in many patients on admission to hospital, without, however, any clinical signs of tetany. Noteworthy differences from the findings among prisoners in Europe were the type of anaemia, a much smaller incidence of diarrhoea in the Indian soldiers, and the much higher incidence of neurological syndromes among them. Accounts of the work have been published (Walters, Rossiter and Lehmann, 1945–6, 1947 *bis*).

## Publications relating to Chapter 5

The following list of references, though including not only the investigations cited above but also numerous studies not specifically mentioned in the text, still does not purport to cover all the British publications dealing with relevant work on nutrition and malnutrition

during the war. Among publications having a direct bearing on the national war-time feeding policy which are omitted from the list are the many emanating from the Food Investigation Board of the Department of Scientific and Industrial Research, the Institute of Statistics at Oxford University and the laboratories of various food manufacturers. For a more comprehensive survey of the literature resulting from war-time studies in this field, reference may be made to Volumes X–XIX of *Nutrition Abstracts and Reviews*.

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# CHAPTER 6

# PUBLIC HEALTH

THE subjects reviewed in this chapter include the research work carried out by members of the Emergency Public Health Laboratory Service in England and Wales, studies of war-time epidemics of diphtheria on Tyneside and at Dundee, work on air-hygiene and the prevention of cross-infection, studies in medical entomology (with special reference to the commoner parasitic infestations met with in Great Britain), administrative arrangements to ensure an adequate supply of essential drugs and immunological agents for Service and civilian needs during the war, and work on the preparation and maintenance of biological standards of potency for many important medicaments; much of the work under the last heading is on an international basis, and it therefore presented special practical difficulties during the war.

## Research Work by Members of the Emergency Public Health Laboratory Service

The origin of the Emergency Public Health Laboratory Service, directed by the Medical Research Council for the Ministry of Health in England and Wales, has been explained in Chapter 1, and accounts of the organisation and work of the Service, and of the analogous arrangements in Scotland and Northern Ireland, are given in other volumes of this History. Here it is necessary only to discuss certain aspects of the research work carried out during the war by members of the Service. For descriptive purposes, this work may be divided into two categories (*a*) group research, (*b*) individual or team research. By group research is meant work carried out on the same subject by two or more laboratories; by individual or team research is meant work carried out on a given subject by one or more workers in the same laboratory. The constitution of the Service lent itself admirably to group research, and numerous problems were investigated in this way.

### GROUP RESEARCH INVESTIGATIONS

*Cerebrospinal Fever.* The epidemic of this disease which occurred in the early part of the war produced the largest number of cases ever notified in the United Kingdom, though the greatly improved treatment, by means of the sulphonamide drugs (see Chapter 7), made the infection much less of a menace than in 1915-17 and the fatality-rate was the lowest on record. Between December 1939 and April 1941,

several studies of the meningococcal carrier condition in the nasopharynx were made in the laboratories of the Service at Cambridge, Cardiff, Colchester, Horsham, Tavistock and Wellington. The subjects examined were soldiers under training, some living in barracks, requisitioned schools or offices, others billeted in private houses. All meningococci isolated were studied serologically and placed in one of five categories: Group I, Group II, Group I + II, Feeble Agglutinators and Inagglutinable. In most of the studies the meningococcal carrier rate in the nasopharynx was high, ranging from 33 to 82 per cent.

The proportion of Group I meningococci isolated varied from 13 to 60 per cent. on different occasions, but in every study Group I constituted the majority of the strains isolated. In Cardiff it was noted that between January and June 1940 (the peak period of the epidemic) the Group I carrier rate was 17·3 per cent. but from July onwards it dropped to 9·1 per cent. Over a period of twelve months, meningococci were isolated on one or more occasions at fortnightly swabbings from 91 out of 102 men (89·2 per cent.) and Group I organisms from 74 men (72·5 per cent.). No case of cerebrospinal fever occurred among the soldiers investigated or among their contacts during the period of study, confirming previous experience that meningococcal infection of the nasopharynx is very common during epidemic times, but that only a small proportion of the infected persons develop meningitis. Studies were also made on the methods of keeping meningococci alive during transport of specimens to the laboratory, and on the effect of adding *p*-aminobenzoic acid to culture media when examining cerebrospinal fluid from patients under sulphonamide treatment.

*Combined Active and Passive Immunisation against Diphtheria.* Though the prophylaxis of infectious disease by combined active and passive immunisation was a common proceeding in veterinary practice, its application to human medicine had not been established at the time of the war. A review of the literature revealed a surprising conflict of opinion on its value, and it was felt that careful quantitative observations were required, preferably on the human subject. A plan of inquiry was drawn up, and observations were made on about 400 undergraduate medical students at Oxford, Cambridge, Sheffield and Liverpool. The antitoxin content of the blood was compared at intervals before and after inoculation in students receiving alum-precipitated toxoid (A.P.T.) alone, and in those given a dose of antiserum at the same time. It was found that in the latter group, provided only a small dose (500 units) of serum was injected, the development of antitoxin was rather slower than in the group receiving only A.P.T., but the ultimate concentration of antitoxin in the blood was not significantly different in the two groups. If, however, a large dose (5,000 units) of serum was injected, not only was there a delay in the appearance of antitoxin in the blood, but the ultimate concentration reached was less than in the group

receiving active immunisation alone (Downie, Glenny, Parish, Wilson Smith and Wilson, 1941).

For the control of institutional outbreaks of diphtheria, the value of combined active and passive immunisation was confirmed. It was found that if all the children were given simultaneous injections of A.P.T. and 500 units of antitoxin, followed four weeks later by a second dose of A.P.T., and if all carriers of the diphtheria bacillus were segregated for six weeks, an outbreak could be brought to an abrupt end without the necessity of closing the school. This method proved most successful in practice (Fulton, Taylor, Wells and Wilson, 1941; Downie, Glenny, Parish, Spooner, Vollum and Wilson, 1948).

*Distribution of Different Types of Diphtheria Bacilli.* Data collected during the years 1941 to 1944 by a number of constituent and associated laboratories of the Service provided information on the distribution of the different types of diphtheria bacilli throughout the country (Reports 1943, 1945). The *gravis* type was usually the commonest, accounting for about 45 per cent. of all strains examined, but in some areas the *mitis* or *intermedius* type predominated. Although the type distribution did not vary greatly during this period, a significant rise in *gravis* type infections was recorded by the Leeds, Lincoln, Northampton, Winchester, Bristol, Cardiff and Carmarthen laboratories, and a significant fall by the Liverpool, Leicester and Exeter laboratories. Where it was possible to correlate changes in the morbidity and case-fatality rates with changes in type distribution, it was found that a rise or fall in the frequency of *gravis* infections was accompanied by a similar trend in the case-fatality rate.

*The Incidence of Cross-infections, Complications and Return Cases in Scarlet Fever.* In view of the importance of cross-infection in surgical wards revealed by hospital bacteriologists in the early years of the war, it was thought desirable to find out what part cross-infection played in the causation of complications and of return cases in scarlet fever. A joint investigation was organised at Oxford, Cambridge and Cardiff, in which repeated cultures were taken from patients in scarlet fever wards and the serological type of the infecting organism was determined. The results showed the danger of generalisation from observations made in any one environment at any one time. Not only did the type distribu-

| | London pre-war figures (Allison and Brown) | Oxford, Cambridge and Cardiff war-time figures |
|---|---|---|
| | per cent. | per cent. |
| Cross-infection rate . . | 70 | 24 |
| Complication rate . . . | 43 | 16 |
| Proportion of complications attributable to cross-infection | 90 | 30 |
| Return case rate . . . | 4·9 | 2·1 |

tion of *Streptococcus pyogenes* vary in the three centres, but the incidence of cross-infection was twice as high in Cardiff as in Oxford. Moreover, the results differed greatly from those obtained in a similar investigation by Allison and Brown in London before the war, as is shown in the table on p. 222.

It will be seen that, in the hospitals included in the war-time study, 70 per cent. of the complications were due to the primary infecting type of streptococcus, and that cross-infection played a relatively small part in their causation. Analysis of the figures revealed also that the majority of complications due to cross-infection occurred from the third week onwards of the patient's stay in hospital. Accordingly, one of the chief conclusions reached from this investigation was that, wherever possible, patients treated for scarlet fever should be discharged from hospital within three weeks.

*Neonatal Diarrhoea.* As part of a concerted attack upon this dangerous infection of newborn infants, arrangements were made at Oxford and Cambridge for a qualitative and quantitative bacteriological study of the faecal flora of healthy contact and non-contact babies, and of babies suffering from the disease. In healthy non-contact babies, lactobacilli constituted about 80 per cent. of the flora and coliform bacilli only about 10 per cent. In sick babies the proportions tended to be reversed; but little diagnostic weight could be placed on these findings, since the same tendency was present in healthy contact babies. No evidence was obtained during the war to incriminate any known pathogenic organism or any known soluble toxin of bacterial origin, but further data, collected since, have redirected attention to the possible significance of certain strains of *Bact. coli.*

*Food Poisoning due to Dried Egg.* By 1941 it seemed likely that, unless extra protein of animal origin were added to the national dietary, serious danger of malnutrition might arise. The Ministry of Food therefore decided to import spray-dried egg from America on a large scale, and the first retail distribution of this substance to the general public took place in July 1942. Examination of the new product soon revealed that a proportion of it was contaminated with organisms of the *Salmonella* group. At the suggestion of the Medical Research Council, an Advisory Bacteriological Committee was set up to help the Ministry of Food in the prevention of disease which might be caused by eating the contaminated material. Arrangements were made for the examination of a large number of samples of dried egg by the Ministry's Laboratory at Cambridge, and by several of the constituent laboratories of the Service, so as to obtain as rapidly as possible information on the frequency and types of the salmonellae present. At the same time a reference laboratory for the determination of *Salmonella* types was established at Oxford. It was found that 10 per cent. of samples of dried egg contained salmonellae, and that the strains isolated belonged to 33

different serological types, the majority of which were new to this country. Following the retail distribution of dried egg, the number of outbreaks of *Salmonella* food poisoning in England and Wales reported to the Service increased from 104 in 1942 to 454 in 1944. The majority of these outbreaks were caused by types of *Salmonella* that had not previously been encountered here. Comparison showed, moreover, that the six types most frequently responsible for food poisoning were the same as the six most frequently found in dried egg. The combined bacteriological and epidemiological evidence left no doubt that much of the increase in food poisoning from 1942 onwards was due to infection from the new product (Medical Research Council, 1947). Early recognition of the danger enabled the Ministry of Food to take precautions and issue instructions designed to minimise the extent and severity of the outbreaks of food poisoning from this cause.

*Other Infections of Man.* The part played by members of the Service in the war-time investigations of the epidemiology of tuberculosis and of the aetiology of infective hepatitis and homologous serum jaundice, has been mentioned in Chapter 4.

*Infection of Cattle with Brucella melitensis.* The isolation by the Stafford Laboratory of the Service, in 1940, of a strain of *Brucella melitensis* from cows' milk occasioned both surprise and misgiving. The organism responsible for contagious abortion of cattle in Great Britain is *Br. abortus*, and no indigenous infection of animals or man with *Br. melitensis* had ever been recorded. Suspicion was aroused by the finding that the herd in question had been inoculated with a vaccine prepared by a firm known to have obtained some of its original material from abroad, and the possibility of bacterial sabotage had to be considered. The Oxford Laboratory, working in conjunction with the Ministry of Agriculture Laboratory at Weybridge, was asked to investigate a number of other herds into which animals sold from the infected herd had been introduced. Several hundred samples of milk from individual quarters of the udder were examined, with the result that two further herds were found to be infected with *Br. melitensis*. All the animals in these herds, as well as those in the original herd, were slaughtered, the supply of the suspected vaccine was stopped, and milk from all herds under investigation was sent to pasteurising depots. No further trouble was experienced and no strain of *Br. melitensis* was subsequently isolated during the war from either animals or man.

## INDIVIDUAL AND TEAM RESEARCH

*Enteric Infections.* The discovery by Felix before the war of the Vi antigen of the typhoid bacillus, and by Craigie of a method of classifying typhoid bacilli into types by means of a series of bacteriophages acting on the Vi antigen, provided a valuable tool for studying the epidemiology of typhoid fever. At the outset of the war Dr. Felix was placed in charge

of an Enteric Reference Laboratory, to which strains of typhoid bacilli from any part of the United Kingdom could be sent for typing. With the help of this laboratory it was possible to show that, in some outbreaks, cases of typhoid fever scattered in different parts of the country but due to the same Vi-phage type of bacillus had been infected from a common source (Felix, 1943, 1944). In this way success was achieved not only in tracking down the origin of the infection, but in proving beyond doubt that a particular carrier was responsible for the contamination of a given article of food. A further extension of this work lay in the application of the Vi-agglutination test to the detection of chronic enteric carriers. It was found that about 90 per cent. of chronic carriers of typhoid bacilli had Vi-agglutinins in their blood serum. In searching for a chronic carrier who was believed to be responsible for an outbreak of typhoid fever, it was therefore found advisable to examine the serum of all suspected persons for Vi-agglutinins before undertaking routine cultivation of the faeces and urine. The practical value of this test is enhanced by the fact that it is independent of the intermittency of excretion of the organisms. The test is also of service in indicating whether a patient convalescent from typhoid is likely to become a chronic carrier.

Research work undertaken during the war led to the finding of Vi-antigens in the paratyphoid B bacillus and in *Salmonella typhi-murium*, one of the commonest organisms met with in food poisoning (Felix and Callow, 1943); it also resulted in the development of a series of bacteriophages acting on the Vi-antigen, by which a subdivision into types, similar to the Vi-phage types of the typhoid bacillus, could be effected. An interesting application of the Vi-phage method of typing was its use by workers at the Cardiff Laboratory for revealing the origin of contamination of water or sewage with typhoid or paratyphoid bacilli.

The practical application of the discovery of the Vi-antigen was not limited to diagnosis. Early in the war Dr. Felix introduced a new method of preparing typhoid-paratyphoid (T.A.B.) vaccine, in which the activity of the Vi-antigen was maintained by the use of 25 per cent. alcohol, instead of heat followed by the addition of 0·5 per cent. phenol, to kill and preserve the organisms (Felix, 1941). Tests made in four of the constituent laboratories showed that the disinfectant action of 25 per cent. alcohol on a variety of bacteria was slightly greater than that of 0·5 per cent. phenol, thus disposing of the criticism that the alcoholised vaccine was unsafe for use. After field trials had been carried out in the Service on the degrees of reaction and of antibody response produced by the new vaccine, it was substituted for phenolised vaccine in the Army and the R.A.F., and in civilian practice.

Work by members of the Service on the early diagnosis of cases of enteric fever and of food poisoning led to the introduction of several new bacteriological media for cultivating organisms of the *Salmonella*

group. One of these contained eosin, brilliant green and methylene blue (Knox, Gell and Pollock, 1942), another brilliant green and acid fuchsin (Hoyle, 1943). Of special interest was the finding by Knox and his colleagues at Leicester that the selective action of sodium tetrathionate lay in its utilisation as a hydrogen acceptor by organisms of the *Salmonella* group. The reduction of tetrathionate by salmonellae formed the basis for developing a valuable culture medium containing this substance (Pollock, Knox and Gell, 1942; Knox, Gell and Pollock, 1943). Another medium devised for the isolation of salmonellae had the particular virtue of suppressing the growth of *Proteus* (Jones and Handley, 1945).

Numerous studies of outbreaks of enteritis among young children in residential nurseries, schools and similar institutions were made by laboratories of the Service. In some of these outbreaks dysentery bacilli of the Sonne or Flexner type were found and in others *Salmonella* strains. In certain instances where no bacteriological agent could be incriminated, infection with the protozoon, *Giardia lamblia*, seemed to be responsible (Ormiston, Taylor and Wilson, 1942), and rapid improvement followed treatment with mepacrine.

*Food Poisoning*. The study of food poisoning due to *Salmonella* organisms in dried egg has already been mentioned. During this investigation six new types of *Salmonella* were discovered: *Salm. cardiff*, *Salm. norwich*, *Salm. horsham*, *Salm. cambridge*, *Salm. shoreditch*, and *Salm. chittagong*.

Apart from salmonella infection, there was a considerable increase in the number of outbreaks of food poisoning attributable either to enterotoxin production by *Staphylococcus aureus* in food, or to toxic substances of undefined nature formed apparently as the result of growth in the food of other species of bacteria. At Oxford, Dr. F. Fulton made a critical study of staphylococcal enterotoxin, and was able to show that the usual method of demonstrating its presence by the injection of kittens was unreliable (Fulton, 1943). He also proved that the enterotoxin was different from the β-lysin, with which it had been identified by some workers. Fractionation studies, controlled by experiments in human volunteers, indicated that the enterotoxin was a proteolytic enzyme, similar in some respects to the lecithinase of *Cl. welchii*. Another advance made in the investigation of staphylococcal infections—not limited to food poisoning—was the development at Oxford of a method of subdividing staphylococci into types by the use of specific bacteriophages (Wilson and Atkinson, 1945). Since 40 per cent. or so of healthy persons carry *Staph. aureus* in the nose or on the skin, it is usually impossible to be certain that any one of a number of food handlers is responsible for contaminating a given food. By the phage-typing method, however, it could often be shown that a given type of staphylococcus was present in the vomit of the patients, in the

suspected food, and in one only of the persons who had taken part in the preparation of the food, thus revealing the human origin of the contamination. Useful work was also carried out on the coagulase reaction and on the production of staphylococcal haemolysin. The type of food poisoning outbreak in which neither salmonella bacilli nor staphylococci could be incriminated presented special difficulty. Evidence collected by a number of laboratories suggested that growth in the food of some non-pathogenic bacteria might, if sufficiently heavy, be accompanied by the formation of toxic substances of undefined nature with an irritant effect on the gastro-intestinal mucosa. Organisms of the aerobic and anaerobic spore-bearing groups came specially under suspicion. Soups, gravies and custards that had been prepared on the previous day, and left overnight at a temperature suitable for bacterial multiplication, were sometimes found to contain enormous numbers of one or other of these groups of organisms; whether the toxic substances were formed by the breakdown of protein in the food or were more closely related to the bacterial cell itself could not be determined. The findings emphasised the importance, particularly in communal feeding, of taking every precaution to limit bacterial growth of any kind in the food.

*Staphylococcal Infections in Maternity Homes.* Pemphigus and conjunctivitis in the babies, and breast abscesses in the mothers, were frequently met with in maternity homes (Hobbs, 1944). The use of the serological and, still better, the phage method of typing staphylococci sometimes led to the identification of a nurse, a midwife, or in one instance a matron, as the source of infection. Mothers tended to be infected by the babies, not the reverse; and examination of breast milk, even in the absence of obvious mastitis, frequently revealed very heavy contamination with staphylococci.

*Diphtheria.* Mention has already been made of the group research on university students into the scientific basis of combined active and passive immunisation. The control of diphtheria presented a serious problem in the early years of the war, and the attention of the Oxford Laboratory, in particular, was directed towards its solution. Groups of school children were injected with alum-precipitated toxoid (A.P.T.) made by different manufacturers, and the results assessed by measuring the Schick-conversion rate (Fulton, Taylor, Moore, Wells and Wilson, 1942). It was found that two doses of 0·1 and 0·3 ml. at four weeks' interval of a good commercial make of A.P.T. resulted in a Schick-conversion rate of about 98 per cent. When free immunisation against diphtheria was introduced by the Ministry of Health towards the end of 1940, the firm making the satisfactory product was temporarily unable to supply all the A.P.T. required for the purpose, and a product of different origin was used to some extent. Observations by the Oxford Laboratory (*loc. cit.*) soon revealed that the Schick-conversion rate in

children immunised with this other product was only 68 per cent., and the batch of A.P.T. was withdrawn as quickly as possible. The poor antigenic potency of this batch was surprising, since it had passed the official tests laid down under the Therapeutic Substances Act. In an investigation into the reason for the failure of the official tests, several batches of A.P.T. of different origin were tested on guinea-pigs and on children, with the result that the Department of Biological Standards at the National Institute for Medical Research was able to devise more stringent conditions for the control of the antigenic potency of A.P.T. It was clear, however, that the behaviour of any given batch in children must remain the final criterion of antigenic potency.

The introduction of sulphonamide and penicillin snuffs by Delafield, Straker and Topley at the London Laboratory of the Service (1941) opened the way for the treatment of carriers of diphtheria bacilli. It was found that the use of sulphathiazole snuff was an effective method of curing the nasal carrier and, to a less extent, the nose and throat carrier. Pure throat carriers, however, proved resistant, and for them tonsillectomy was still the only satisfactory method of treatment.

For the rapid bacteriological diagnosis of diphtheria a new tellurite-blood agar medium was developed in the Cardiff Laboratory of the Service (Hoyle, 1941); Dr. Hoyle also made a study of the antigenic structure of diphtheria and diphtheroid bacilli and demonstrated the presence in them of three different lipoid antigens detectable by the complement-fixation test (Hoyle, 1942).

*Whooping Cough.* As soon as diphtheria immunisation had been established on a satisfactory basis, attention was turned to the problem of preventing whooping cough by vaccination. This was very much more difficult, partly because immunity to whooping cough appears to be mainly antibacterial rather than antitoxic, and partly because the disease is liable to affect infants at a very early age, before active immunisation can be successfully undertaken. Workers in the Oxford Laboratory carried out carefully controlled trials of a whooping cough vaccine in residential nurseries, and in children attending infant welfare clinics and day nurseries. The results of this first series of tests were very disappointing, and gave little evidence of protective power in the vaccine. There was no obvious reason why children inoculated in this country should not have benefited from the vaccine when so many favourable reports of whooping-cough vaccination had been published in the U.S.A. and Canada. Further work on the subject since the end of the war has met with much greater success.

*Fungus Infections.* In relation to the programme of the Committee on Medical Mycology set up by the Medical Research Council in 1944, a survey of the extent, character and gravity of fungous diseases in Great Britain was undertaken from the Winchester Laboratory of the Service (Duncan, 1945). Requests for material from known or suspected

mycoses yielded about 1,500 specimens, some of which, however, were not of mycological interest. Among the grave systemic mycoses encountered was histoplasmosis—the first case diagnosed in Europe and only the second in the Old World. Later a second case of histoplasmosis was identified, and a study was made of the fungus *Histoplasma capsulatum* from the two cases. Other systemic mycoses encountered were torulosis of the central nervous system and also in the generalised and subcutaneous forms; chronic sporotrichosis; and many cases of actinomycosis caused by the anaerobic *Actinomyces bovis* Harz, and some by the semi-acid-fast *Nocardia asteroides* group. Mucormycosis, affecting the brain, the lungs and other organs or tissues, was diagnosed in histological preparations from six cases, but from only one was a culture of the infecting fungus available; the infection seemed usually to be of haematogenous distribution. Many examples of moniliasis were studied; the dermal form, including paronychia, was not uncommon, and an observation was made of the unfavourable effect of local penicillin treatment in a series of cases of otitis media complicated by 'Monilia' infection. It was inevitable that the dermatomycoses should have provided the greater number of specimens, and these revealed an unexpectedly high incidence of *Microsporum canis* (the common parasite of dogs and cats) in tinea capitis of children in the south-western counties. In a number of villages in South Devon *M. canis* var. *felineum* predominated, to the apparent exclusion of *Microsporum audouini*: and in Portsmouth, where, despite the reduction of the child population by war-time evacuation, attendances at the ringworm clinic reached the highest number for about twenty years, the only dermatophyte found in the indigenous infections was *Microsporum canis* var. *lanosum*. Fifty per cent. of the specimens from tinea capitis in the London area yielded *M. canis* var. *felineum*. There was clear evidence of transmission of the animal *Microsporum* from child to child, but it is probable that the number of transmissions in series is limited and that frequent renewal from the animal host is necessary for the continued propagation of the disease on children. In the industrial Midlands the predominating cause of tinea capitis was the common parasite of children, *M. audouini*, and in epidemics of ringworm in South Wales, East Anglia and Hertfordshire this species was the only fungus found. While infections by *M. canis* are usually much more easily cured than those by *M. audouini*, and may not require X-ray treatment, they introduce a new problem in epidemiology and control.

An investigation of tinea pedis in members of the Fighting Services showed, at first, a relatively high incidence of *Epidermophyton floccosum*, but, later, isolations of *Trichophyton interdigitale* increased notably, and finally, with the inclusion of personnel returning from South-East Asia, a large proportion of the specimens yielded *Trichophyton rubrum*.

## Diphtheria on Tyneside and at Dundee

The severe outbreaks of diphtheria which occurred on Tyneside and at Dundee during the war years led to important epidemiological and immunological investigations in both areas. The results, obtained by different methods and approach, were found to be closely similar and mutually supporting and have since been published as a joint report (Hartley, Tulloch, Anderson, Davidson, Grant, Jamieson, Neubauer, Norton and Robertson, 1950).

An unexpected feature of both epidemics was that at times more than one-third of the cases on Tyneside, and one-half of those at Dundee, occurred in persons who had received a full and apparently satisfactory course of prophylactic inoculation; some of these patients, when admitted to hospital, had a titre of circulating antitoxin largely in excess of that usually considered adequate for protection.

The course of the disease was, however, found to be very different in the inoculated and the uninoculated. In the inoculated the illness was nearly always mild and the case fatality was nil, whereas among the uninoculated the case fatality was 11·0 per cent. in 1943 and 5·9 per cent. in 1944 on Tyneside, and 9·5 per cent. between October 1941 and October 1942 at Dundee. A possible explanation of the finding that inoculated persons might contract the disease but were protected against its severer manifestations was provided by the Tyneside work, in which examinations of serial samples of serum from inoculated persons, who had not been Schick-tested or given antitoxin as a therapeutic measure, showed that the titre of circulating antitoxin was low at the onset of the disease and then increased rapidly, sometimes to phenomenally high levels, under the stimulus of infection, slowly declining again over a period of months.

## Air Hygiene and the Prevention of Cross-infection

In the years immediately before the war there was a noticeable re-orientation of ideas about the mode of spread of respiratory infections. Flügge's view that direct droplet spray infection was the only important mode of transmission had long been accepted, although early work by French and German investigators, particularly in tuberculosis, had pointed to the significance of dust as a vehicle, and epidemiological studies in this country had suggested that infections such as measles and chicken-pox could be carried considerable distances. Griffith's publication in 1934 on the subdivision of *Streptococcus pyogenes* into some thirty serological types gave a fresh impetus to the study of streptococcal infections. The demonstration by Cruickshank, a year later, that the same serological type of streptococcus was present in the dust and air as was found infecting burns in a special burns ward was followed by further circumstantial evidence

incriminating dust in the spread of such streptococcal infections as puerperal sepsis and septic complications of scarlet fever. Meanwhile, in the U.S.A., W. F. Wells, a sanitary engineer, was evolving new ideas about the importance of minute droplets (called by him droplet nuclei) in the spread of respiratory infection. He claimed that droplets of 0·1 mm. or less in diameter, expelled during talking, coughing and sneezing, were so small or quickly became so by evaporation that, instead of falling quickly to the ground, they remained suspended in the air for varying periods and might thus be conveyed some distance from their source. He further suggested, on the basis of experimental work, that ultra-violet light could be used to control this form of air-borne infection. Another line of approach was the attempt at aerial disinfection with suitable bactericides, such as sodium hypochlorite and resorcinol, which when finely sprayed as 'aerosols' could considerably reduce the bacterial content of the air and of surfaces on which they fell.

### STUDIES IN AIR HYGIENE DURING THE WAR

With these new fields being opened up it was natural that the war should stimulate more intensive research into methods for the control of respiratory infections, since it was realised that there might be much overcrowding of communities under unfavourable conditions, not only among recruits in training but also among civilian populations as a result of evacuation from the large cities and the use of underground shelters during air-raids. A team of workers at the National Institute for Medical Research, led initially by the late Sir Patrick Laidlaw and after his death by Dr. C. H. Andrewes and Dr. R. B. Bourdillon, proceeded to examine some of the problems of air-borne infection, at first experimentally and later in the field. Laboratory research was carried out on methods for measuring bacterial pollution of the air and of testing the efficiency of air disinfectants under experimental conditions, and field observations were made on different methods of disinfecting the air, together with an evaluation of the conditions affecting the practical utility of air disinfectants.

For measuring the bacterial content of the air, the slit-sampler (Bourdillon, Lidwell and Thomas, 1941), in which air was drawn at a fixed rate through a narrow slit to impinge on a plate of culture medium rotating on an enclosed platform, proved remarkably efficient and adaptable. It had the advantages over the broth or bubbler type of sampler favoured in America, that many samples of air could be taken by the same machine within a short time; that the actual number of bacteria-carrying particles in the air was determined and their size estimated by comparing the colony count with the numbers that settled naturally on an open plate; and that sudden variations in bacterial contamination of the air, as might happen during the changing of a surgical dressing (see Bourdillon and Colebrook, 1946), were

readily detected. The rate of 'killing' of bacterial clouds by different aerial disinfectants could also be readily gauged with the slit-sampler (Bourdillon, *et al.*, 1948).

Various studies carried out under both experimental and field conditions confirmed the belief that the smaller bacteria-carrying droplets expelled from the respiratory tract could remain suspended in the air for periods up to half an hour, while activities such as bedmaking and sweeping raised into the air a large number of bacteria, a varying proportion of which could be identified as respiratory pathogens, including the haemolytic streptococcus and *Staphylococcus aureus*. Attempts to keep indoor air clean were therefore directed along three lines (*a*) the use of masks to prevent the dissemination of droplets from the respiratory tract; (*b*) dust suppressive measures applied particularly to floors and fabrics, and (*c*) the use of aerial disinfectants.

*Masks.* Bourdillon and his colleagues (1948) gave some attention to the design of masks which could be used either to prevent droplets of all sizes being sprayed into the air during talking, coughing or sneezing, or alternatively to deflect the spray from being projected directly at those in close proximity, so as to minimise the spread of respiratory infections, e.g. influenza, among 'shelter' populations. For the first of these purposes the efficiency of masks as bacterial filters was tested in a special chamber in which the masked operator talked, coughed or sneezed while samples of air were tested for the extent of bacterial contamination. It was noted that a close-fitting gauze mask of two layers of 80 threads per inch was much more retentive than an eight-layer mask of 22 threads per inch, but that no mask was completely impervious to the 'spraying spit' which is the equivalent of a sneeze. For deflection of the bacteria-carrying particles, plastic masks made of cellulose acetate were designed; these were either of the simple Yashmak type or moulded under the chin and fitted with a spectacle frame. Such masks were comfortable to wear and the moulded masks were particularly successful in preventing bacteria-carrying particles being sprayed forward or downward during ordinary talking and breathing.

*Dust Suppression.* The use of oiled surfaces and fabrics, to which dry or moist bacteria-carrying particles would adhere, was developed by van den Ende and his colleagues (1940, 1941). They found that spindle oil (a crude petroleum oil) could, when sparingly applied to unpolished wooden floors or linoleum, absorb dust particles, fluff from blankets and so on, and thus prevent their being air-borne during sweeping or other dust-raising activities. However, in scarlet fever and E.N.T. wards the bed linen was shown to be the main reservoir of streptococcus-contaminated dust, so that a practical method for oiling blankets and sheets had to be devised. This was successfully accomplished by using an oil-in-water emulsion, consisting of technical white oil plus a cationic

or anionic wetting substance such as cetylpyridium bromide or sodium lauryl sulphonate, which fixed any desired amount of the oil in woollen or cotton fabrics and could be adapted for use in hospital laundries (Harwood, Powney and Edwards, 1944). When tested in measles wards where there was a high incidence of secondary streptococcal infection, the oiling of floors and fabrics practically eliminated streptococcal contamination of the air during bed-making and sweeping, and quickly reduced the streptococcal cross-infection rate to small proportions (Wright, Cruickshank and Gunn, 1944). These dust-suppressive measures were later adapted and improved by Puck and others, in America, who also confirmed their value in controlling the spread of streptococcal ward infection; however, oiled floors and blankets were ineffective in preventing outbreaks of acute respiratory disease, probably of virus origin, which were common among American recruits in training camps. These findings suggest that dust-suppressive measures are likely to be more effective in controlling the intramural spread of bacterial respiratory diseases such as streptococcal infection, diphtheria, and possibly tuberculosis, than the corresponding virus diseases, although there is evidence that many respiratory viruses and rickettsiae (e.g. those of influenza, psittacosis and Q fever) may resist natural drying and initiate infection as dust-borne particles. The prevention of air pollution by infected dust particles is a desirable concomitant to aerial disinfection, since large dry particles are particularly resistant to the action of ultra-violet light or bactericidal vapours, although Garrod (1944) showed that natural daylight, even when transmitted through glass, has a considerable bactericidal action on contaminated dust.

*Aerial Disinfection.* If the droplet nuclei of Wells are important in the spread of respiratory infections, this mode of transmission should be largely controllable by a high ventilation rate to dilute the infected air-borne material below the limit of the infecting dose, or by some system of aerial disinfection. Since, however, a rapid turnover of fresh air is not encouraged in the season when these diseases are most prevalent, the workers at the National Institute turned their attention to various artificial means of disinfecting the air—in particular, the use of certain chemical substances vaporised in the air and, to a less extent, ultra-violet light and heat. They confirmed the work of Masterman on the disinfecting action of sodium hypochlorite finely sprayed into the air and agreed that the action was due to the liberation of hypochlorous acid gas (Edward and Lidwell, 1943). The early view of Trillat, supported for some time by Twort and his co-workers (1940, 1942), that the action of these so-called aerosols was due to the collision between them and the bacteria-carrying particles was proved erroneous by Robertson and others in the U.S.A. in their work with the glycols. Instead, these substances act by condensing from the vapour phase on

to bacteria-carrying particles, so that the most active aerial bactericides will be those that have a high and rapid 'killing' rate in aqueous solution, a high solubility in water and a low vapour pressure. In addition, of course, aerial disinfectants must be free from toxicity, irritation, odour and corrosiveness, and should preferably be easily vaporised and also cheap. These requirements suggested to Lovelock, Lidwell and Raymond (1944) that lactic acid and similar α-hydroxy-acid compounds might be useful aerial disinfectants, and so it proved. One particular substance, α-hydroxymethylbutyric acid, which could be vaporised at room temperature, was found to give promising results when tested in a mess-room (Bourdillon *et al.*, 1948).

Ultra-violet light, unlike the chemical bactericides, acts better in a dry than in a moist atmosphere, but like them is relatively ineffective against large bacteria-carrying particles. Its use as an aerial disinfectant in occupied spaces must be limited to an irradiated 'ceiling' at a height of 7 ft. or more to avoid direct exposure, or as 'curtains' of light to replace doors or partitions in hospital wards. For 'ceiling' disinfection, its efficacy depends on care in placing the lamps (usually on walls), keeping them clean and bactericidally efficient, and ensuring a good vertical circulation of air. In field trials, ultra-violet light was found not greatly to reduce the total bacterial count, but its use has been suggested where poor ventilation is combined with opportunities for dissemination of fine droplet nuclei containing pathogenic viruses or bacteria freshly sprayed from the respiratory tract. Wells and his colleagues in America claimed some success with it in controlling the epidemic spread of measles, mumps and chicken-pox in schools.

Other studies in air hygiene included sampling of the air in different semi-closed communities, e.g. factories, hospitals and naval vessels, with the suggestion that the total bacterial count might be used as an index of ventilation, and that 50 bacteria-carrying particles per cubic ft. of air might be considered a satisfactory upper limit in any ordinary occupied space (Bourdillon *et al.*, *loc. cit.*). Preliminary experiments on air-borne infection, using a U-shaped duct to eliminate direct projectile transmission, were carried out on ferrets, which could be infected with measurable doses of air-borne influenza virus in varying particle sizes; while, in another specially designed chamber, the infecting dose by inhalation of *Myco. tuberculosis* (or other organisms) could be determined with remarkable accuracy (Andrewes and Glover, 1941; Glover, 1941, 1944).

Although in this brief survey prominence has been given to work at the National Institute for Medical Research, other studies, e.g. by Twort and his colleagues (*loc. cit.*) on aerial disinfectants, particularly resorcinol, and by Challinor (1943) and Duguid (1946) in Edinburgh on the use of the glycols and on the characterisation of sprayed droplets and droplet nuclei, likewise deserve mention. Relevant work was also

carried out at the Ministry of Supply Experimental Station at Porton (see Davies, 1946; Barnes, 1947).

### HOSPITAL INFECTION

Hospital infection may be defined clinically as respiratory, gastro-intestinal, wound, skin or mucous membrane infection, contracted in hospital during the course of another disease. However, laboratory examination has shown that overt infection represents only a small proportion of the total cross-infection, which, bacteriologically, implies the acquisition by a patient of pathogenic micro-organisms not present on admission to hospital. The particular type of hospital infection that claimed first attention during the war years was the infection of war wounds in the Services and among civilian air-raid casualties (see Chapter 3). The studies of Miles *et al.* (1940) showed that secondary or 'added' infection of extensive wounds, particularly with *Streptococcus pyogenes*, coliform organisms, and to a less extent *Staphylococcus aureus*, was common, and the evidence indicated that, with less extensive wounds, the infection was transferred most often from already infected surfaces by contact with soiled fingers, instruments, dressings, lotions, etc., and less frequently from the nose and throat of dressers or from contaminated dust. The 'no touch' technique designed to obviate these risks was found to reduce to a minimum the occurrence of secondary infection in open wounds (McKissock, Wright and Miles, 1941), and was also applied successfully in the control of infection of civilian injuries treated either in the wards or the out-patient department at the Birmingham Accident Hospital, where the Medical Research Council established special Wound Infection and Burns Research Units (Gissane, Miles and Williams, 1944; Williams *et al.*, 1944). For extensive burns, where air-borne infection is a greater hazard than with wounds of smaller area, a specially designed dressing station into which clean and conditioned air could be introduced under pressure was found to have advantages, and in combination with penicillin treatment it resulted in a great reduction in the incidence of secondary infection (Bourdillon and Colebrook, 1946).

The more general problem of cross-infection in hospitals for sick children, infectious disease, maternity cases, E.N.T. conditions, etc., was considered by a sub-committee of the Preventive Medicine Committee of the Medical Research Council (Appendix I), which issued a War Memorandum on the subject (Medical Research Council, 1944); the memorandum has been widely used for the instruction of nursing and medical staffs in the source, modes of spread and control of hospital infection. Reference has already been made to the use of masks, oiled floors and bed linen for the control of secondary streptococcal infection. Two further relevant points may be mentioned: during the war the importance of the nasal streptococcal carrier as a source of infection

became recognised (Hare 1941; and other workers), while Garrod, as already noted, showed that daylight, even through glass, had a bactericidal effect on pathogenic bacteria.

Considerable progress in the control of intestinal infection in hospitals resulted from the introduction of the selective culture medium, deoxycholate-citrate agar (Hynes, 1942), which revealed the high incidence of symptomless and convalescent carriers during outbreaks of bacillary dysentery and *Salmonella* infection. This finding, together with the efficacy of sulphaguanidine and other sulphonamide compounds in securing early bacteriological as well as clinical cure in bacillary dysentery, has been successfully applied to the eradication of this disease from mental hospitals, where it used to be so prevalent (Anderson and Cruickshank, 1941).

## Medical Entomology

In the First World War the serious problems of trench fever and epidemic typhus led to much research on methods for controlling the responsible insect vector, the louse. Field delousing procedures were introduced, but because of the continual reinfestation that occurred, it was impossible to eliminate the risk of these louse-borne infections; none of the chemicals then used to destroy lice gave protection for more than a couple of days.

Early in 1940 work aimed at finding an insecticide with more lasting effect was started in the Department of Entomology at the London School of Hygiene and Tropical Medicine under the direction of Professor P. A. Buxton. Dr. J. R. Busvine carried out trials with lethane preparations (thiocyanates) on infested tramps. By impregnating seams in their undergarments with insecticide, it was found possible to keep the tramps virtually free from lice for as long as one month, provided that the garments were not washed. To obviate this unhygienic condition, a light-weight body belt, woven in such a way that it was covered with folds, was specially designed by the Cotton Research Board. When suitably impregnated with lethane, this belt proved efficient; but it had the disadvantage that, if sweating were excessive, some skin irritation was liable to occur. In 1942, successful field trials of the lethane belt were organised among native labour forces in the Eastern Mediterranean. At that time there was much epidemic typhus among civilians and in the labour corps; the belts were used on a large scale by the Army and reported on favourably. The troops themselves were almost free of lice, and military cases of typhus were very few and sporadic. By the end of 1943, after the landing in Italy, the risk to the soldier was perhaps greater, but by then D.D.T. powder was available in adequate amounts and the lethane belt was not needed. An important use for lethane preparations in Great Britain was based on their incorporation into a hair dressing which became

known as lethane hair oil (Busvine and Buxton, 1942). The Ministry of Health arranged tests of this mixture for the treatment of head louse infestations, and it was subsequently included in the National War Formulary.

In parallel with these studies, work was carried out in Professor Buxton's department on the use of safer alternative methods to hydrogen cyanide for delousing infested clothing (Busvine, 1943, 1944; David, 1943, 1944).

In December 1942, the possibilities of D.D.T. as an insecticide were brought to the notice of entomologists in Britain and America. Tests of its action against lice showed it to have advantages over any known insecticide, and arrangements were made for its large-scale production. One important point in which D.D.T. excelled lethane was that it was not readily washed out of impregnated garments. The part subsequently played by D.D.T. in checking the Naples typhus epidemic is well known, and, as a result of its use on impregnated garments, the troops engaged on the Continent of Europe after D-day were kept virtually free of lice.

Research on the mosquito vectors of malaria, and on the use of repellents and insecticides against them, has been discussed in Chapter 4; studies of the part played by *Trombicula* mites in the epidemiology of scrub typhus have also been mentioned in that chapter. A brief account of the work of the Entomological Sub-committee of the Military Personnel Research Committee is given in Chapter 2, and a summary of the work on insecticides undertaken by the Chemical Defence Research Establishment of the Ministry of Supply is included in Chapter 10.

*Bed-bug Infestation.* The report of a Committee on this subject, set up by the Medical Research Council at the request of the Ministry of Health in 1935, was published in 1942. It summarised five years' work on different aspects of the problem, and had an appendix dealing with the eradication of bed-bugs from air-raid shelters. When D.D.T. became available, the possibilities of bed-bug extermination were greatly enhanced, and research was undertaken at the London School of Hygiene and Tropical Medicine to determine the best methods of using the material (Barnes, 1945 *ter*). The residual toxicity of D.D.T. films on surfaces such as cement, plaster, glass and woodwork was examined; the use of distempers or paints containing D.D.T. was also investigated, but this method proved unsatisfactory.

*Scabies.* Towards the end of 1940, the Ministry of Health made a grant for work on scabies by Dr. Kenneth Mellanby at the Sorby Research Institute, Sheffield. These funds were used to establish the Institute—in a converted private house—and to engage the services of up to twenty men, all conscientious objectors to military service, who were willing to serve as subjects for experiments on the transmission and prevention of scabies. In 1942 the Medical Research Council

assumed financial responsibility for the programme of the Institute, which included not only the scabies studies but also important nutritional experiments (on the vitamin A and vitamin C requirements of human adults) as described in Chapter 5.

The work on scabies began in 1941. Preliminary investigation of the incidence of the disease showed that a steep rise had started in 1936, and that the increased incidence in war-time was only the continuation of a trend which had been apparent some years earlier.

It was shown that scabies is usually transmitted by intimate personal contact and that transmission by fomites is rare. As a result of this finding, the disinfestation of bedding, a troublesome and expensive procedure, has largely been abandoned, attention being concentrated, instead, upon the persons infested and those who live in immediate contact with them.

The course of the disease on initial infestation was shown to differ greatly from that following subsequent infestation. In a first attack, multiplication of the parasites progressed for about a month before the patient was aware of any symptoms. At about this time a true sensitisation developed, as judged by inoculation experiments, and itching became progressively more troublesome; the latter provoked scratching and consequent septic lesions of the skin. The combined effect of sepsis, scratching and the host's immune reaction was to decimate the parasite population, which thereafter persisted at a low level unless the parasites were exterminated completely by treatment or occasionally by spontaneous cure. If a second infestation occurred, symptoms developed within twenty-four hours, due to the rapid re-activation of the host's immune reaction; in these subsequent attacks, the parasite rate never reached the high levels recorded in primary infestations. Experimental re-infestation of cured cases was much more difficult to achieve than infestation of persons who had no immunity.

The various medicaments which have been used against scabies were critically tested, and observations were made of their effect on the mites in the skin. It was shown that when properly applied, one treatment with benzyl benzoate would cure the disease in almost every case, and that routine disinfestation of clothing and bedding was unnecessary.

Accounts of the researches in scabies at the Sorby Research Institute have been given in two books (Mellanby, 1943, 1945); references to scientific papers dealing with various aspects of the work are included in the list of publications at the end of this Chapter.

### Supplies of Antitoxins, Vaccines and Important Drugs

(*A*) *Antitoxins and Vaccines*: In 1937 the Medical Research Council were entrusted by the Government with responsibility for organising and co-ordinating supplies of certain immunological agents of special importance in war-time. The original object had been provision against

the possibility of bacteriological warfare or sabotage, but actually the largest task was the supply of great quantities of tetanus and gas-gangrene antitoxins for use in the wounded. At a later stage the questions arose of supplying vaccine protection against louse-borne typhus and, in the Far East, against mite-borne scrub-typhus. Apart from needs arising specially from the war, moreover, the Council had eventually to deal with supplies of materials for prophylaxis against diphtheria and, on a smaller scale, against measles.

At the outset of their work in this field the Council appointed an Immunological Supplies Committee, under the chairmanship of the late Sir John Ledingham (Appendix I), to survey the existing supply position, and to estimate future requirements of the more essential agents for Service and civilian use in emergency. Technical advice throughout the scheme was given by Dr. (now Sir Percival) Hartley and his colleagues in the Department of Biological Standards at the National Institute for Medical Research, while the ready co-operation of the manufacturers, both in rapidly increasing the supplies of particular products to meet the estimated demands, and in carrying out *ad hoc* research on relevant problems, was at all stages invaluable; special acknowledgement is due in this respect to the Lister Institute of Preventive Medicine and the Wellcome Foundation.

The first problem demanding urgent attention was the provision of tetanus antitoxin in quantity sufficient to meet the mobilisation requirements of the Fighting Services and the expected needs of the civilian population under air attack. At the time when the Committee began work, the Army had obtained all the tetanus antitoxin available in the country and had made plans for its replenishment. This was satisfactory so far as it went, but it was clear that a very large increase in production was necessary, particularly in regard to the expected requirements for civilian casualties. After careful consideration, it was decided that the needs of a pressing situation could best be met by supplying most of the additional antitoxin required for prophylaxis in the form of 'natural' serum. The adoption of this policy not only made it possible to reach the target set with the least possible delay, but also resulted in important economies in materials and expenditure; by the time of the Munich crisis a million prophylactic doses were available, and initial stocks had been distributed to over forty civilian centres in Great Britain and Northern Ireland. Less than a year later, and before the actual outbreak of war, a further and more extensive distribution was made, and it can be recorded that from this time there was never any risk that supplies would fall short of the home needs.

The decision to issue natural serum for the prophylaxis of tetanus was taken with full knowledge of its theoretical disadvantages as compared with the refined and concentrated product, particularly in regard to keeping properties and liability to cause serum reactions. In practice,

however, few reports were received of serum reactions after injections of the natural serum. Allowance for decline in potency of the serum was made by stipulating that when issued it should contain a 30 per cent. excess of antitoxin units, and at a later stage by increasing the volume of the dose in the case of the older preparations. The problem of the stability of the antibodies in natural antitoxins was the subject of much research in the United Kingdom during the war; it was examined in respect of diphtheria and staphylococcus antitoxins by Llewellyn Smith (1939 *bis*), of tetanus antitoxin by Amies (1945) and Hartley (1945), of diphtheria and tetanus antitoxins by Glenny (1945), and of gas-gangrene antitoxins by Bruce White (1945). The results were reassuring. The stability of refined antitoxins was similarly studied by Harms (1945).

It is of interest to recall that the establishment of the Serum Drying Unit at Cambridge (described in Chapter 3) had its origin in a proposal to dry stocks of tetanus antitoxin, since dried antibodies are known to be almost indefinitely stable. The proposal was not implemented on a large scale, however, and the Unit was adapted to the no less important task of producing large quantities of dried serum and plasma for resuscitation work.

In addition to the extensive issues of natural tetanus antitoxin for prophylaxis, already mentioned, considerable stocks of the refined and concentrated antitoxin were ordered for the same purpose, so as to make the best use of existing manufacturing facilities in the country and to ensure that alternative sources of supply would be available in case of need. All the tetanus antitoxin for therapeutic purposes, for which there was a much smaller demand, was supplied as the refined and concentrated product.

Arrangements for providing large stocks of polyvalent gas-gangrene antitoxin (against *Cl. welchii*, *Cl. septicum* and *Cl. oedematiens* infection) were likewise made, and in this case the technical problems were in some respects more difficult to solve. Opinion was divided as to the value of gas-gangrene antitoxin, particularly for prophylaxis, but the material had nevertheless to be supplied in a form suitable either for prophylaxis or for treatment, and the composition and appropriate dosage decided empirically in the absence of precise knowledge on these points; material concentrated by the usual ammonium sulphate process was issued in the early years of the war. On the recommendation of the Anaerobes Sub-committee of the War Wounds Committee the dosage was later increased and the relative proportions of the components altered; the volume of the doses being kept small by changing to material refined by peptic digestion. These modifications necessitated a very considerable new expansion of production, the more so in view of the steadily increasing use of the antitoxin for prophylaxis as evidence of its value accumulated (see Chapter 3).

The Medical Research Council had meanwhile made further arrangements with the manufacturers for the continued production of tetanus and gas-gangrene antitoxins for both Service and civilian requirements on a war-time scale, and large reserves were accumulated and held in a common pool. Detailed distribution was in the hands of the respective Departments, but the Council were in a position to co-ordinate and anticipate the varying demands from all quarters. This scheme remained in operation until 1943, when responsibility for issuing the materials was transferred to the Ministry of Supply. Up to the date of the transfer, the Council distributed from the pool approximately 4,500,000 prophylactic doses and 118,000 therapeutic doses of tetanus antitoxin, and over 380,000 bottles of polyvalent gas-gangrene antitoxin, each containing one therapeutic dose (or the equivalent in terms of prophylactic doses).

The Council were also charged with the responsibility of acquiring reserve stocks of certain vaccines and sera, to supplement supplies ordinarily available, for the control and treatment of epidemic diseases in the civilian population during war-time. The products in question were typhoid-paratyphoid, cholera and dysentery vaccines, and anti-anthrax, anti-dysentery, anti-plague and anti-typhoid sera. In the event, the need to use these materials for the control of epidemics did not arise, but it was necessary to augment existing stocks of typhoid-paratyphoid vaccine, and to plan for further production, following the decision of the Ministry of Health, late in 1940, to issue this vaccine free to local authorities for the immunisation of key personnel in the Civil Defence Forces.

Anti-anthrax serum, which was not made in this country before the war, presented a special problem, and in this case it was deemed advisable to supplement the existing reserves by arranging for its production on a limited scale.

In relation to the campaign inaugurated by the Ministry of Health towards the end of 1940 for the mass immunisation of children against diphtheria, the Medical Research Council were asked at short notice to organise the supply and distribution of the necessary prophylactics. In the early months of the campaign very great difficulty was experienced in keeping pace with demands for material, but the rapid response of the home manufacturers, helped out by a generous gift from the American Red Cross Society, soon enabled supply to overtake demand. Thereafter the flow of production was maintained and adjusted in accordance with current requirements; but further steps had to be taken to deal with technical and administrative problems which arose, particularly in relation to the manufacture and testing of alum-precipitated toxoid, and to the determination of the optimum dosage for effective immunisation.

In 1941, at the request of the Service Departments and the Ministry of Health, the Council undertook to arrange for the supply and

distribution of typhus vaccine required for the protection of Service personnel and of civilians specially exposed to the risk of the louse-borne (or laboratory) infection. It was decided to obtain supplies of vaccine made by a method involving the use of fertile eggs and, as it was impracticable to manufacture such a vaccine in this country on a large scale, the necessary quantities had to be ordered from the United States and Canada. In making these arrangements the Council had valuable help from the Rockefeller Foundation of New York.

Towards the end of the war, the large-scale production of scrub-typhus vaccine was undertaken in this country, as already mentioned in Chapter 4.

In association with the Ministry of Health, the Medical Research Council were also concerned with obtaining supplies of three other immunological products not ordinarily available commercially in the United Kingdom. These were botulinum antitoxin, rabies vaccine, and human adult serum for the prophylaxis of measles in children; the arrangements made, under the last heading, to collect large quantities of human serum have been described in Chapter 3.

With the exception of tetanus and gas-gangrene antitoxins, and scrub-typhus vaccine, distribution of all the products mentioned above to civilian Departments was made through the Emergency Public Health Laboratory Service.

(*B*) *Important Drugs*: At the outbreak of the First World War, the state of preparedness in Great Britain in regard to the replacement of valuable drugs manufactured solely in Germany was regrettably low. There developed very quickly, for example, a serious shortage of the German product salvarsan, which was needed for the treatment of syphilis. To obviate similar difficulties in the event of a second world war, Government action through the Committee of Imperial Defence had been taken in advance to ensure the accumulation of adequate stocks of various natural and synthetic medicaments of foreign origin.

To maintain a satisfactory supply of the more important synthetic drugs and diagnostic agents hitherto obtainable only from enemy countries, it was necessary to arrange for chemical equivalents of many of these products to be manufactured in Great Britain, under Government licence where applicable. The Medical Research Council were largely concerned with these arrangements, which were made through the Association of British Chemical Manufacturers or in appropriate cases direct with individual firms. A fundamental principle adopted was that the British equivalents should be manufactured and sold under non-proprietary names. Among the products tested clinically under this scheme were mepacrine and pamaquin as identical substitutes for the German 'Atebrin' and 'Plasmochin', respectively (see Chapter 4); bromethol for 'Avertin', soluble hexobarbitone for 'Evipan sodium', iodoxyl for 'Uroselectan-B', pheniodol for 'Biliselectan', and pethidine

for 'Dolantol' or 'Dolantin', which had been introduced just before the war as a synthetic substitute for morphine; the clinical tests of pethidine were sponsored mainly by the War Wounds Committee (see Chapter 3).

### THE THERAPEUTIC REQUIREMENTS COMMITTEE

As a result of the preparatory action taken by the Government, as outlined in the preceding section, considerable stocks of important drugs and other medicinal agents had been accumulated in the United Kingdom before the war. To ensure that these supplies were used economically and to the best advantage in medicine, and that satisfactory arrangements were made to maintain and augment them, an advisory body called the Therapeutic Requirements Committee (Appendix I) was appointed by the Medical Research Council at the request of the Ministry of Health; by arrangement with the Ministry of Agriculture and Fisheries, the committee's terms of reference were extended later to cover also the needs of veterinary practice. The committee worked in close relationship with the Directorate of Medical Supplies in the Ministry of Supply, as well as with the Ministries of Health and Agriculture, the British Pharmacopoeia Commission, the Pharmaceutical Society and the Insurance Acts Committee of the British Medical Association; Dr. C. H. Hampshire, the Secretary of the British Pharmacopoeia Commission, served as its Secretary.

The committee advised the controllers of the import and manufacture of drugs as to which drugs were vitally necessary and must be supplied at all costs. It informed the medical and veterinary professions, and those responsible for the formularies, indents and quotas, as to which medicaments were scarce and must be used economically; it published the names of British equivalents for foreign drugs; it dealt with the problems which inevitably arise when any form of restriction is practised, and indicated where exceptions should be made to avoid hardship.

The first business of the committee was to prepare a list of drugs in common use, classifying them both as to therapeutic value and availability in war-time. A memorandum on the subject, prepared in the light of the information made available to the committee from various sources, was published (Medical Research Council, 1941); this document and certain other lists prepared for special purposes were adopted as guides for preparing the National War Formulary used in the Emergency Medical Services and by the medical services of the Fighting Forces and of the Colonies, as well as for the assistance of the Import Licensing Department of the Board of Trade. A second edition of the memorandum, issued in 1944, contained an appendix dealing with methods of disinfection, and with desirable measures of war-time economy in the use of bactericides.

Under an addition made in 1941 to the Defence Regulations, the Minister of Health and the Secretaries of State for the Home Department and for Scotland were empowered, after consultation with the Medical Research Council, to make Orders, during the war, dealing with the replacement of scarce drugs by alternatives, and authorising pharmacists receiving prescriptions including scarce drugs to supply instead the alternatives named in the Orders, unless the doctor writing the prescription had specified that no alternative was to be used. In fulfilling their statutory function in this matter, the Council had the advice of the Therapeutic Requirements Committee. Shortages of drugs during the war were in many cases due to the armament programme. Alcohol, glycerin and mercury were required for munitions, and phenolic compounds for plastics. Other important drugs came under the control of the Ministry of Food and the Petroleum Board. Manufacture of drugs might be further restricted by shortages of labour and plant. In all such instances, steps had to be taken to ensure that the needs of medical and veterinary practice were properly estimated and adequately covered. Less controllable shortages were due to difficulties of importation, and to the fact that so many countries on which the United Kingdom had previously relied for the supply of vegetable and synthetic drugs were occupied by the enemy. In 1942, Japan overran the Dutch East Indies, thereby securing 95 per cent. of the world's cinchona production and leaving the United Nations with little more than a year's supply of quinine. Supplies of agar, so important in bacteriological work, were also cut off, as this was at that time almost a complete monopoly of the Japanese. These difficulties had to be met by the substitution of alternatives wherever possible, and the conservation of existing stocks for the purposes for which they were vitally necessary, as for example the limitation of quinine to the treatment of malaria.

Very early in the war it became imperative to study means of conserving supplies of certain substances which, though widely prescribed, act as flavours or vehicles rather than as therapeutic agents; substances in this category were sugar, alcohol, glycerin, syrups, oils and fats. Reduction or omission of these materials entailed a radical change in the prescription of medicines and in the dressing of wounds and of skin diseases. Tinctures gave place to tablets and watery extracts; toothpastes and cough mixtures acquired a war-time austerity. Ointments and creams constituted a particularly difficult group, owing on the one hand to the shortage of glycerin, fats and starch, and on the other to the much increased demand for anti-dermatitis creams, anti-gas ointments, wound and burns dressings, mosquito repellents and applications for the treatment of parasitic infestations.

An entirely new kind of problem was set by the advance in chemotherapy which had begun in 1935. This is exemplified by the history of the sulphonamides, in which successive improvements due to research

led through sulphanilamide, sulphapyridine and sulphathiazole to sulphadiazine and sulphadimethylpyrimidine, with the side developments of sulphaguanidine and succinylsulphathiazole. The problem was strictly comparable with the progressive improvement of aircraft and weapons of war, and it gave rise to the same difficulty in production programmes; sometimes there were special difficulties because of the need to obtain raw materials, such as calcium cyanamide, from abroad; from the point of view especially of the supply position, the Therapeutic Requirements Committee had an important share in preparing the Medical Research Council War Memorandum on the medical use of sulphonamides, which is mentioned in Chapter 7. Examples of other therapeutic innovations which gave rise to supply problems of varying degrees of complexity were the replacement of sulphur by benzyl benzoate in the treatment of scabies, the sequence of safrol, lethane and finally D.D.T. in the treatment of louse infestations, and the series thiourea, thiouracil and methyl thiouracil in the treatment of hyperthyroidism. In all these matters it was the function of the committee to warn the Ministry of Supply of impending changes based on sound scientific evidence, and at the same time to discourage mere fashions in prescribing which did not justify the cost of alterations in schedules.

The more permanent effects on prescribing produced by the committee's activities during the war were in general the acceleration of changes which would have come more gradually in peace-time, an acceleration which was the result of expert direction and the avoidance of vested interests or unsupported tradition. Single substances and active principles were used instead of tinctures and mixtures; the many hospital pharmacopoeias, each with its favourite prescriptions, were replaced by the National War Formulary of the Ministry of Health, and the use of foreign or proprietary names for drugs was discouraged. Synthetic chemicals were substituted for galenical remedies. Bismuth salts gave way to magnesium trisilicate and aluminium hydroxide in the treatment of dyspepsia, boric lint was replaced by the sulphonamides and later penicillin, and the production of unnecessary varieties of hypnotics and local anaesthetics was temporarily checked. It can fairly be argued, therefore, that the conditions of war-time austerity which necessitated the committee's work were by no means wholly deleterious to medical and veterinary practice.

The committee was discharged on the completion of its war-time task, most of its functions which were applicable to post-war conditions being taken over by a new Drug Requirements Committee appointed by the Minister of Health.

## Biological Standards

The outbreak of war threatened the work, and even the continued existence, of the Permanent Standards Commission of the League of

Nations—the body which had hitherto co-ordinated the arrangements made in Great Britain and other countries for the preparation, maintenance and issue of international standards of potency for many important medicaments, including antitoxins, hormones, vitamins, and certain essential drugs such as the arsphenamines. The substances covered by the scheme had this in common, that their activity could be measured only by biological tests; most of them, moreover, were administered by injection, which necessitated sterility. The value of an international scheme for the standardisation of such products needs no stressing; it assists both the manufacturer and the doctor, and protects the patient. The Department of Biological Standards at the National Institute for Medical Research, London, had taken a leading part in the work of the Permanent Standards Commission from its inception, and the Institute had been entrusted by the Commission with custody of the international standards for drugs, hormones and vitamins. Inevitably, therefore, the war-time interference with the Commission's activities placed exceptional responsibilities upon the Institute.

In the years immediately preceding the war, National Control Centres for the distribution of international standards, and in some cases also for their local preparation, had been established in various countries. When war seemed imminent, the great practical utility of these centres was emphasised. In the spring of 1939, large stocks of all the international standards maintained at the National Institute for Medical Research were despatched to each of the National Control Centres; there is good reason to believe that, as a result of this action, most countries were adequately provided throughout the war with the international standards for which the Institute in London was responsible. As an additional security, six separate consignments of the international standards were at different times sent to Geneva; in this way, supplementary stocks were available in Switzerland to meet any shortages which might occur in countries having no direct access to supplies from the United Kingdom. To minimise the risk of destruction by air attack of the international standards maintained at the National Institute, sets of the standards were dispersed to several depots throughout England.

The seizure of Denmark by Germany in April 1940, created special difficulties, for the State Serum Institute in Copenhagen had been entrusted by the Permanent Standards Commission with the maintenance of the international standards for antitoxins, antisera and tuberculin. Loss of access to the serological standards would have been very serious, because of the war-time demand for tetanus and gas-gangrene antitoxins for the wounded. Fortunately, large stocks of all these standards, or their exact equivalents, were normally kept at the National Institute in order to fulfil obligations of the Medical Research Council to the Ministry of Health in respect of the Therapeutic Substances

Act, as well as to the British Pharmacopoeia Commission and to Governments of the overseas Dominions where the British Pharmacopoeia was operative. Accordingly, when a request from the League of Nations was received for the provision of the antitoxin and antiserum standards to countries which could no longer obtain their supplies from Copenhagen, it was possible for the Institute in London to meet the demand, and thus this valuable international service was maintained throughout the war.

In the summer of 1940, when Great Britain was menaced by invasion, further precautions seemed desirable to preserve the international biological standards from loss and, with them, the international units. Stocks of the antitoxin and antiserum standards, sufficient to permit the reproduction of the international units in case of need, were therefore transferred to Canada, cold storage and laboratory accommodation being provided by the Department of Pensions and National Health, Ottawa. In addition, a detailed description of the laboratory and other procedures which would be necessary in order to replace the serological standards was prepared at the National Institute, and copies of this document were deposited for safety with the International Health Board of the Rockefeller Foundation in New York, and with the Departments of Pensions and National Health, Ottawa.

It is satisfactory to record that progress in the field of international biological standardisation did not cease with the coming of war, despite the fact that the international body, under which this work is normally carried out, had ceased to function. It is no less satisfactory to be able to report that the emergency action on standardisation questions taken by the Department of Biological Standards at the National Institute, in the absence of advice from the international body, was endorsed after the war by the Expert Committee on Biological Standardisation of the World Health Organisation, which has assumed the functions of the Permanent Standards Commission of the former League of Nations.

Perhaps the most important task which fell to the lot of the Department of Biological Standards during the war was work in connexion with the establishment of an international standard for penicillin. The urgent need of such a standard became evident with the increased production and use of penicillin which occurred in 1944; there was a real risk at that time that different 'units' of penicillin might become current in Britain and America, with all the uncertainty and confusion that would involve. An international conference on the subject was held in London, under the chairmanship of Sir Henry Dale, the only member of the Permanent Standards Commission who was available; it was attended by delegates from Great Britain, the United States, France, Australia and Canada. Preparatory work on the dispensing of samples for assay, and in the arrangement of preliminary comparative investigations in eight different laboratories in Great Britain, the United States and Canada, was undertaken by the Department of

Biological Standards. On the basis of the evidence thus adduced, it was agreed to adopt pure crystalline sodium penicillin II as the international standard, the unit of activity being defined as that contained in 1/1,666 mg. of the international standard—a value very close to that of the 'Oxford Unit' originally proposed by Florey and his co-workers. The report of the proceedings of the conference, giving the evidence on which the decisions were based, was prepared by the Department; it was published as one number of the *Quarterly Bulletin of the Health Organisation of the League of Nations*, and subsequently approved by the World Health Organisation.

Other new international standards established under war-time emergency arrangements, and later confirmed by the World Health Organisation, were those for vitamin E and heparin (Department of Biological Standards, National Institute for Medical Research, 1940–1; 1942–3; Hume, 1940–1; McIntosh, 1942–3). In addition, the existing international standard for vitamin $B_1$ was replaced by pure synthetic aneurin instead of the cruder material which had been used hitherto (Macrae, 1940–1). The pure crystalline β-carotene used since 1934 as standard for vitamin A became exhausted and had to be replaced by a freshly prepared supply. Other standards needing replacement during the war were those for the extract of the posterior lobe of the pituitary gland, for many of the sex hormones, and for the antitoxins to the anaerobic organisms of the gas-gangrene group. In the studies relating to vitamin standardisation, the Department of Biological Standards had the invaluable co-operation of expert sub-committees of the Accessory Food Factors Committee, whose other work during the war is noticed in Chapter 5. Advice on the mathematical aspects of vitamin standardisation was given by Dr. J. O. Irwin of the statistical staff of the Medical Research Council.

The Department of Biological Standards continued during the war its primary function of carrying out research into improved methods of measuring the biological activity of medicinal agents. It also supplied standardised materials for some important field investigations, including the tuberculin used for the Prophit Survey of the Royal College of Physicians on the incidence of tuberculous infection in young adults (see Chapter 4).

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# CHAPTER 7

# SULPHONAMIDES: AND THE DEVELOPMENT OF PENICILLIN

## War-time Research on the Sulphonamides

THE sulphonamide drugs had been used clinically on a considerable scale for about five years before the outbreak of war. By 1939 the value of sulphanilamide against haemolytic streptococcal infections was well established and sulphapyridine, though introduced only in the previous year, had already become the standard treatment for pneumococcal pneumonia; infection with meningococci, gonococci, and coliform bacteria (in the urinary tract) were also recognised as commonly susceptible to sulphonamide treatment; it had been shown that sulphanilamide exerted a direct bacteriostatic effect *in vitro* and that this action could be neutralised by extracts of tissues, bacteria or yeast.

### INTRODUCTION OF NEW COMPOUNDS

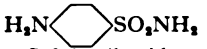
Sulphapyridine, although very effective in the treatment of pneumococcal pneumonia, which had proved resistant to sulphanilamide, had the disadvantage of causing nausea and vomiting in a high proportion of the patients in whom it was used. During the period 1939–43, several other compounds were brought into clinical use which were decidedly less toxic than sulphapyridine and also had higher activity. The first of these, sulphathiazole, was described independently by workers in America and in Europe. It was synthesised in Great Britain in February 1938, in the laboratories of May and Baker, Ltd., by whom a patent application was lodged in June 1938, and to whom a British Patent (No. 517,272; Newbery and Viaud) in respect of this and related compounds was granted early in 1940. At first this drug attracted little attention, since in mouse tests against streptococci and pneumococci it seemed to possess little or no advantage over sulphapyridine when given in equal doses. This was because of the rapid excretion of sulphathiazole, and its consequently low blood concentration; when the rapidity of excretion was recognised and allowed for, the valuable potentialities of the drug became apparent; in addition to being effective in pneumococcal pneumonia, and much less liable than sulphapyridine to cause gastric disturbance, sulphathiazole was found to have some therapeutic activity in staphylococcal infections, against which sulphanilamide and sulphapyridine were useless.

The next few years saw the successive production in America of sulphadiazine, sulphadimidine (sulphadimethylpyrimidine) and sulphamerazine. Sulphadimidine was at first ignored in America, since it was

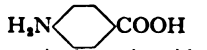
feared that its methyl groups might produce peripheral neuritis; its introduction into general clinical use was due to researches carried out by workers in the Imperial Chemical Industries, Ltd., laboratories in Manchester and by Macartney *et al.* (1942), who demonstrated its value in pneumococcal pneumonia; it was issued in the United Kingdom under the trade mark 'Sulphamezathine'. All these compounds are characterised by diminished toxicity and by persistent high blood concentrations resulting from comparatively small doses.

## MODE OF ACTION OF THE SULPHONAMIDES: SULPHONAMIDE ANTAGONISTS

It had been known for some time that the direct bacteriostatic action of sulphanilamide could be neutralised by extracts of tissues, of bacteria or of yeasts. Woods (1940) showed that these extracts contained a substance resembling *p*-aminobenzoic acid, and that pure *p*-aminobenzoic acid in quite small concentrations inhibited much greater concentrations of sulphanilamide. From the similarity in the chemical structure of these two compounds:



Sulphanilamide



*p*-aminobenzoic acid

Fildes (1940) evolved the theory that *p*-aminobenzoic acid is an essential metabolite of the bacterial cell and that sulphanilamide blocks the enzyme systems which utilise it, by 'competitive interference'. This theory won general acceptance and the same concept was applied to other fields, e.g. the interference with the utilisation of pantothenic acid by the presence of pantoyl taurine, which resembles it in chemical structure (McIlwain, 1941, 1942; McIlwain and Hawking, 1943). The study of this aspect of sulphonamide action afforded a new insight into the ways by which chemotherapeutic agents work.

Substances antagonistic to the antibacterial action of most sulphonamides have been shown to occur in pus and necrotic tissue; consequently sulphonamides may exert less effect than usual if they are applied locally to wounds containing pus or sloughs. Inhibiting substances have also been demonstrated in muscle, spleen and pancreas, and in pleural, pericardial and synovial fluids, and these substances may possibly interfere with the therapeutic action of the drugs *in vivo*. Besides *p*-aminobenzoic acid itself, other chemical compounds containing the aminobenzoate group can antagonise the action of sulphonamides, although less rapidly. Notable among these are the local anaesthetics procaine and benzocaine (Woods, 1940). It is doubtful how far the injection of procaine in the neighbourhood of a local infection under treatment with sulphonamides really hampers the therapeutic effect of the drugs, for the procaine does not persist for long; but it is obviously wiser to use a local anaesthetic which does not contain the

amino-benzoate group, and thereby avoid the possibility of inhibition. Moreover, since procaine gives the same colour reaction with Bratton and Marshall's test as do the sulphonamides, the former should not be used in the collection of biological fluids, e.g. cerebrospinal fluid, required for the estimation of their sulphonamide content.

### LOCAL APPLICATION OF SULPHONAMIDES TO WOUNDS

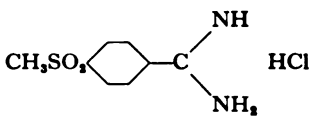
The first published account of the local use of sulphonamides to control wound infection in man was that of Jensen, Johnsrud and Nelson in America, who in 1939 reported success in preventing infection in compound fractures by the insertion of sulphanilamide. With the outbreak of war, the treatment of wounds became a problem of vital importance, and the potentialities of sulphonamides for this purpose were energetically investigated by the French workers, Nitti, Legroux, Chorine and others. The results achieved were encouraging, but unfortunately the field application of their studies was brought to an abrupt end by the military disasters which overwhelmed their country. However, the subject was taken up with vigour by Colebrook and other workers with the British Army (see Chapter 3), who showed that infected superficial wounds and burns could be freed from haemolytic streptococci by this means. Since these organisms are among the most dangerous of all secondary invaders of wounds, the conclusive demonstration that they could be easily suppressed by sulphanilamide in situations where they were accessible to local treatment constituted an important advance. The use of sulphonamides for the treatment of wounds by local application became widespread during the period 1941–3. Later, it was discovered that the application of sulphonamides to the skin might result in sensitisation to the drugs, and doubts began to arise as to their efficacy in the local treatment of wound infection except where the wounds were very superficial. By the end of the war the routine application of sulphonamides in powder form as a dressing for wounds and burns had been largely replaced by the local and systemic use of penicillin.

### TREATMENT OF GAS GANGRENE

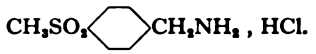
In the early years of the war it was shown that sulphonamides had a considerable protective action in animals experimentally infected with the organisms of gas gangrene, especially if the drugs were given together with antitoxin. In these experiments mice were injected intraperitoneally or intramuscularly with the organisms, and were treated with sulphonamides systemically or by intramuscular injection (Stephenson and Ross, 1940; Henderson and Gorer, 1940). Alternatively, experimental wounds were made in guineapigs, the organisms were inserted and the wounds were then packed with single sulphonamides or with sulphonamide mixtures (Hawking, 1941, 1942; and

other authors). From these experiments it was concluded that *Cl. welchii* and *Cl. septicum* were fairly sensitive to sulphonamides, but that *Cl. oedematiens* was almost insensitive; sulphathiazole and sulphadiazine were the most active sulphonamides tested for the purpose. Treatment by local application was much more effective than systemic administration; any delay in applying the sulphonamide after the wound had been infected greatly diminished the percentage of animals which survived. In contrast with the numerous papers relating to experiments with animals, there have been remarkably few reports on clinical cases of gas gangrene in human subjects treated with sulphonamides. From experience with air-raid casualties it became clear that gas gangrene could develop in patients who had been treated systemically and locally with the drugs; but there were no reliable figures to indicate whether or not the use of sulphonamides prophylactically had diminished the frequency with which gas gangrene occurred. Later (1944) it was recommended that cases of threatened gas gangrene should be treated with penicillin rather than with sulphonamides.

In the laboratory, Evans, Fuller and Walker (1944) showed that considerable action against clostridia was exerted by the sulphone compounds *p*-methylsulphonylbenzamidine hydrochloride (V 187)




and *p*-methylsulphonylbenzylamine hydrochloride (V 335)




The former compound could control experimental infections of guineapigs by *Cl. welchii*, *Cl. septicum* or *Cl. oedematiens* if injected intramuscularly at the site in which the clostridia had been injected not more than five hours previously. The action of these compounds—like that of *p*-sulphonamidobenzylamine or 'Marfanil', which had been used by the Germans against gas gangrene—is not antagonised by *p*-aminobenzoic acid. It proved difficult to obtain information as to the value of these compounds in the treatment of human cases of gas gangrene, and the success of penicillin discouraged further investigation (see also Chapter 3).

### TREATMENT OF MISCELLANEOUS INFECTIONS

In the early years of the war much work was published on the treatment of streptococcal, pneumococcal and other systemic and local infections with the newer sulphonamides. Reference to some of these studies will be found in various chapters of the Medicine and Pathology volume of the Official Medical History; a general account of the state of

knowledge of the medical uses of sulphonamides at two different stages of the war is given in a Medical Research Council War Memorandum by numerous authors, of which the first edition was published in 1943 and a second, revised edition in 1945. Many of these studies were of general, rather than specifically war-time importance, and they need not be detailed here, particularly since the use of sulphonamides for infections responding also to penicillin has to a considerable extent been superseded. Among conditions for which the value of sulphonamides is still unrivalled are cerebrospinal fever (meningococcal meningitis) and bacillary dysentery (see below); the drugs are widely used against coliform infections of the urinary tract, and are very effective in chancroid. They are commonly given for the prophylaxis of streptococcal infections, and used both pre-operatively and post-operatively in the surgery of the intestinal tract.

Brief reference has been made in Chapter 4 to field tests of the antimalarial action of sulphonamides, and the use of sulphathiazole and penicillin snuffs to treat nasal carriers of diphtheria bacilli has been noticed in Chapter 6. War-time researches on the use of sulphonamides or sulphones to treat certain other diseases—e.g. the important studies of the value of sulphones in leprosy—are omitted from discussion in this volume, as having had no direct relationship to the war effort.

### CEREBROSPINAL FEVER

Some important studies of the sulphonamide treatment of cerebrospinal fever were made by workers in the United Kingdom during the war years (Banks, 1939, 1941, 1948; Harries, 1942; Joe, 1942); and they firmly established the value of these drugs against meningococcal infections; a useful report, summarising the current state of knowledge of the subject, was issued by the Department of Health for Scotland in 1944. A general account of progress in knowledge of cerebrospinal fever during the war is given in the volume of this History dealing with Medicine and Pathology. Investigations of the epidemiology and bacteriology of the disease have been mentioned in Chapter 6 of the present volume.

### BACILLARY DYSENTERY

The greatest war-time advance in the practical application of sulphonamides in medicine was their very successful use in the treatment of bacillary dysentery. This disease was formerly of major military importance, and its specific cure by means of sulphonamides was a conspicuous triumph. The achievement was due mainly to the work of Marshall and his collaborators in the United States, who introduced sulphaguanidine—a compound prepared and described in 1938 by Buttle and others in the United Kingdom— as a means of attacking coliform and dysentery bacilli in the lumen of the intestine. The value

of this drug in bacillary dysentery was demonstrated in Great Britain by Anderson and Cruickshank (1941), who treated 41 cases of Flexner dysentery occurring in a mental hospital and compared them with 55 untreated controls. Treatment was begun on the second to fifth day after the onset of symptoms. In the severe cases treated, blood and mucus persisted in the stools for an average of 1·8 days; in the controls, for 3·8 days. The further use of sulphaguanidine was developed by Fairley and Boyd (1943) and other workers in oversea theatres of war. Fairley and Boyd reported the treatment of 371 severe cases of dysentery in the Middle East, of which 135 were due to Shiga's bacillus. There was a great improvement of clinical symptoms within 24 to 48 hours; this was associated with a fall of the temperature and pulse rate to normal within 1 to 3 days, a remarkable reduction in the number of stools to 1 or 2 per day within 5 to 6 days, rapid disappearance of blood from the faeces and a slow disappearance of mucus. The use of sulphaguanidine revolutionised the treatment of dysentery among the Allied forces in the Middle East; subsequent experience showed that other sulphonamides, at first sulphapyridine and later sulphathiazole and sulphadiazine, were also effective in bacillary dysentery; the war period further saw the introduction, for the treatment of intestinal infections, of two derivatives of sulphathiazole—succinylsulphathiazole and phthalylsulphathiazole—which, unlike the parent substance, are absorbed to but a limited extent; both were introduced in America.

SKIN INFECTIONS (*See also* Medicine and Pathology volume.)

Sulphathiazole ointment was at first widely recommended as a local application for the treatment of impetigo and similar conditions. Later it was found that the application of sulphonamides to the skin, especially in eczematous subjects, often led to the development of sulphonamide hypersensitivity (Park, 1943, 1944; Tate and Klorfajn, 1944); and the local use of these drugs for skin infections had been almost abandoned by the end of the war.

GONORRHOEA (*See also* Medicine and Pathology volume.)

In the early stages of the war the sulphonamides were used extensively and with conspicuous success in the treatment of gonorrhoea among the armed forces, though the development of drug resistance often limited their usefulness. Later the sulphonamides were displaced by penicillin for this purpose.

### ACQUIRED RESISTANCE TO SULPHONAMIDES

The problem of sulphonamide resistance in micro-organisms was extensively investigated during the war. It was found that bacteria could become resistant to these drugs if exposed to them in subeffective concentrations *in vitro* or *in vivo*, just as trypanosomes become resistant

to arsenicals after prolonged exposure to their action in subeffective dosage. Sulphonamide resistance is important clinically in the case of gonococci, and of haemolytic streptococci in wounds; in respect of other organisms, it probably develops only rarely in the course of therapy. Simple methods for detecting and measuring sulphonamide sensitivity and resistance in bacteria were devised by Colebrook and his co-workers (Harper and Cawston, 1945).

### TOXIC EFFECTS OF SULPHONAMIDES

Numerous investigations were undertaken on the toxic and other harmful effects of various members of the sulphonamide group of drugs. The most frequent major harmful effects encountered were:

(i) *Blockage of the urinary passages* by the deposition of crystals of sulphonamides and their acetyl derivatives. Many experiments were done to elucidate the physical factors concerned, e.g. solubility, effect of pH of urine, etc.

(ii) *Sensitisation to sulphonamides*, resulting in drug fever, skin rashes and similar conditions. Much clinical information was collected about these phenomena, but in general they did not lend themselves to experimental study.

(iii) *Blood changes*. Cyanosis resulting from the use of these drugs was shown to be unimportant, and the restrictions formerly laid down against the giving of eggs and saline purgatives during sulphonamide therapy were abandoned. On the other hand, agranulocytosis and haemolytic anaemia were recognised as of grave importance, although little new evidence about their mechanism of causation was forthcoming during the war.

### ESTIMATION OF SULPHONAMIDES IN BLOOD

A rapid clinical method devised by Fuller (1942) for estimating the concentration of sulphonamides in the blood was found very useful in practice.

## The Development of Penicillin

The successful development of penicillin as a protective and curative agent against many dangerous infections was the outstanding medical event of the war. In addition to its unique value for the saving of life and limb, the drug has great historical importance in having been the first really satisfactory member—from the medical point of view—of the seemingly unlimited series of naturally occurring anti-microbial agents now known as the antibiotics.

To appreciate the various steps which led to the introduction of penicillin into medical and veterinary practice, it is necessary to bear in mind two facts. Firstly, the concept of microbial antagonisms was not in itself novel in 1928, when Fleming made his original observations

on the bactericidal effect of penicillin; from the early days of bacteriology there had been recorded in the literature a number of examples of natural antagonism between micro-organisms, and on more than one occasion attempts had been made to use this phenomenon as a basis for preparing therapeutic agents to combat infection; products of *Ps. pyocyanea* had received special attention in this way at the beginning of the century; all these attempts to use antibiotics for medical purposes had failed, however, because of the excessive toxicity of the products examined. Secondly, Fleming was one of the group who worked with Sir Almroth Wright during the First World War, on the actions of the antiseptics then favoured for wound treatment; they reached the conclusion that many of these substances were at least as toxic to leucocytes and tissue cells as to bacteria; consequently, Fleming was already on the look out for an effective antibacterial agent which was free from this disadvantage, and he was quick to grasp the potential importance, at least as a wound dressing, of a substance such as penicillin which apparently combined strong antiseptic power with harmlessness to the cells of the host.

### PIONEER STUDIES OF PENICILLIN BY FLEMING AND OTHERS

It was in 1929 that Professor (now Sir) Alexander Fleming, working at St. Mary's Hospital, London, reported his discovery that the accidental contamination of a staphylococcal culture with a mould (later identified as *Penicillium notatum*) had led to dissolution of the staphylococci by some substance produced by the mould; he had cultivated the mould in broth and found that, after the mould had grown for a few days, the broth was capable of preventing the growth of a number of pathogenic organisms, principally Gram-positive—some of them even when the broth was diluted 800 times, though others were insusceptible. This broth Fleming called 'penicillin', a name later to be applied to the inhibitory substance itself. It was shown that the broth was a slow-acting type of antiseptic, and that 20 c.c. of it could be injected intravenously into a rabbit, and 0·5 c.c. intraperitoneally into a mouse, without producing more reaction than did uninoculated broth. Other experiments showed that the penicillin-broth was no more toxic than ordinary broth to leucocytes *in vitro*, and Fleming noted that this was the first antiseptic he had encountered which was considerably more harmful to bacteria than to tissue cells. He suggested that the broth might be a useful dressing to apply locally to infected tissues, and some patients with septic wounds were so treated. However, the results were not sufficiently definite to stimulate further work. Fleming's experiments, and others carried out by Raistrick and his colleagues at the London School of Hygiene in 1932, disclosed that penicillin was difficult to manipulate chemically, and it was described as a 'very labile substance', a view confirmed by Reid in 1935. Fleming recognised

that he had under investigation an antiseptic with unusually good properties, but the crucial point which has made penicillin so important in medicine, namely, the demonstration that when circulating in the blood it is a chemotherapeutic agent of remarkable antibacterial potency and remarkably low toxicity, was only to be arrived at later—following the comprehensive investigations begun at Oxford ten years after the original announcement of the discovery of penicillin and when any idea that the substance might be of use in medicine had been virtually abandoned. It should be remembered that the idea of antibacterial chemotherapy was much less familiar in 1929 than it became later, as a result of the introduction of the sulphonamides.

### START OF THE WORK AT OXFORD

The sequence of events which led to the work on antibiotics in the Sir William Dunn School of Pathology at Oxford began in 1930, when Professor (now Sir) Howard Florey and his colleagues started to examine the properties of lysozyme, an antibacterial enzyme widely distributed in animal tissues, which had been described by Fleming in 1924. These researches lasted several years, and led to the purification of the enzyme. In 1939, in the course of discussions on lysozyme and on the phenomenon of microbial antagonism, Chain and Florey decided to undertake jointly a systematic investigation of some of the antibacterial substances produced by micro-organisms—including *Penicillium notatum*, *Ps. pyocyanea* and *B. subtilis*. This work was planned before the outbreak of war, when there was no idea that penicillin was likely to play an important part in the treatment of battle injuries. The research was envisaged primarily as an academic study, with possibilities of considerable theoretical interest. It was started in 1939 by Chain and Falk with a culture of Fleming's strain of *Penicillium notatum*, which had been maintained for some years in the School of Pathology, Oxford, for other purposes, and it was taken up more intensively by Chain, Florey and Heatley in the autumn of 1939. Soon the work on penicillin became so absorbing that studies of the products of *Ps. pyocyanea* and *B. subtilis* were suspended. After some initial experiments had given encouraging results, a team of workers was assembled for the various phases of the penicillin research. It consisted of Professor Florey, Dr. Chain, Professor A. D. Gardner, Dr. N. G. Heatley, Dr. E. P. Abraham, Dr. M. A. Jennings, Dr. J. Orr-Ewing, Dr. A. G. Sanders, and later, for the clinical work, Dr. C. M. Fletcher and Dr. M. E. (now Lady) Florey. The Medical Research Council, the Rockefeller Foundation of New York and the Nuffield Trust contributed to the cost of the programme.

First the mould was grown on the medium proposed by Raistrick and his colleagues, and the production of antibacterial activity was confirmed. Next a simple biological test was devised, by means of which

the results of extraction and other chemical procedures could be followed. This test, now known as the cylinder plate method of assay, proved of great practical value at all stages. The succeeding steps which led to the preparation of a stable dry powder were: (i) extraction of the penicillin into ether from the acidified crude broth by the method which had been described by Raistrick and his co-workers in 1932, (ii) extraction of the penicillin from the ether into dilute alkali or buffer solution at about pH 7, and (iii) lyophile drying of the neutral aqueous solution. Subsequently, other solvents were used instead of ether.

With the preparation of concentrates free from protein and inorganic salts, the way was open for further development of the research programme. A preliminary study of the chemical properties of penicillin was made (see Chapter 9), the principal reasons for the lability of the drug were established, and stable salts were prepared. The antibacterial capacity of the successive extracts was examined. The growth of *Staphylococcus aureus* and *Streptococcus pyogenes* was inhibited by one part in 1,000,000 of one of the first dry preparations, while the gonococcus was even more sensitive to its action. Many other organisms were sensitive to high dilutions, but *Bact. coli* and other Gram-negative bacilli were found to be in various degrees resistant. Besides obtaining further quantitative information on the relative sensitivity of different bacteria, the workers at Oxford were able to make some important additions to the list of sensitive and resistant organisms which Fleming had tested with his broth filtrate. In particular it was shown that the clostridia of gas gangrene and a strain of *Actinomyces bovis* were sensitive to penicillin, and that the tubercle bacillus was not. While these antibacterial properties were of interest, the drug would have been of little practical value unless its power had been retained in the presence of the constituents of normal and inflamed tissues. All the sulphonamides known at that time were largely or completely inactivated by the constituents of pus and other breakdown products of the tissues, and were active in the presence of a relatively small number of organisms only. It was shown that penicillin, a substance of an entirely different nature, retained its full activity in the presence of pus, blood serum and tissue autolysates, and that variations in the size of the inoculum of bacteria had comparatively little influence on its inhibitory powers.

### PROTECTIVE EXPERIMENTS IN ANIMALS

In May 1940, the first attempts were made to ascertain whether an extract of the *Penicillium* exerted any protective effect on mice infected with streptococci. As the active material was at that time both scanty and precious, these experiments were of limited scope; nevertheless, the results were hopeful, and useful indications were obtained as to the size and frequency of dose, and the duration of treatment, necessary to produce the optimum effect. On the basis of this information, a further

series of tests was carried out in the summer of 1940, and these proved conclusively that penicillin injected subcutaneously could protect an animal from an infection induced by injecting staphylococci or streptococci intraperitoneally, which would ordinarily have been fatal; the animals showed no toxic symptoms from the injections; the same method of treatment was effective against lethal doses of spores of *Cl. septicum* injected intramuscularly (Chain, Florey *et al.*, 1940).

Thus a new property of penicillin was disclosed: it was shown to be a true systemic chemotherapeutic agent—that is to say, when absorbed into the blood-stream after administration it would arrest a distant or generalised infection without itself doing harm to the animal. Among the experiments made at this time were a series dealing with the behaviour of penicillin towards living tissues *in vitro* and *in situ*. Whereas staphylococci were inhibited by the early crude preparations at about one part in 1,000,000, human leucocytes *in vitro* remained active in a one in 1,000 solution for at least three hours. Later, it was shown by Medawar and by Jacoby that there was the same large gap between the concentration that produced bacterial inhibition and that which interfered with the growth of tissues in culture. Pharmacological investigations in animals all reinforced the view that the extracts were remarkably free from poisonous effects. It was also established that penicillin was absorbed from the subcutaneous tissues, muscles and small intestine, and was rapidly excreted in the urine. It was subsequently demonstrated that penicillin appeared in the bile of animals, but not in substantial amounts in the cerebrospinal fluid, tears or pancreatic juice.

From these observations and from the concurrent chemical investigations (Chapter 9), considerable knowledge was obtained of the behaviour of penicillin in the body, so that, even before the first patient was treated, the lines along which therapy would have to be planned had been formulated. For instance, the rapid excretion of penicillin in the urine made frequent or continuous injections imperative if an effective level of the drug was to be maintained in the blood; the destruction of penicillin by acid was a contra-indication to giving it by the mouth, and the discovery that it could be destroyed by certain bacteria emphasised the need for maintaining sterility.

### UNIT OF PENICILLIN ACTIVITY

At an early stage it became clear that to express the potency of the various extracts, a system of units would be much more convenient than the use of such terms as '15 milligrams of material inhibiting *Staph. aureus* at 1 in 640,000 but not at 1 in 1,280,000', etc. A particular buffer solution of partially purified penicillin was therefore taken as a standard, and the unit was defined as the amount of penicillin contained

in 1 ml. of this solution. This unit was afterwards almost universally adopted by workers with penicillin, under the designation of the 'Oxford Unit'. Later, the International Penicillin Unit, proposed at a conference convened on behalf of the Permanent Standards Commission of the League of Nations Health Organisation in October 1944, and subsequently approved by the World Health Organisation, was fixed at approximately the same value (see also under Biological Standards, Chapter 6).

### EARLY EFFORTS TO INCREASE PRODUCTION

Because penicillin was formed only in minute amounts in the metabolism fluid of the fungus, production in the laboratory, by the improvised methods at first available, was very slow, and it seemed that the only way to get enough material for further progress at reasonable speed was to seek the aid of a commercial firm. The first approach of this nature was made from Oxford in July 1940, but soon afterwards one of the worst periods of the air war against the United Kingdom began, and, because of this and other difficulties in industrial production, it was decided to endeavour to brew and extract at Oxford sufficient material for pilot trials in human diseases; it was realised that unless clinical results could be obtained which were as striking as those recorded in the animal experiments, it was highly improbable that any firm would embark on really large-scale production of penicillin. The difficulties in raising the scale of laboratory production were formidable; it was necessary to decide whether it would be more profitable to try to accumulate material from the small yield per litre which was then obtainable, until enough had been made for trial in man, or whether to hold up production while a search was made into possible means of increasing the yield. The former policy was adopted—probably rightly, as it was only after the first demonstration of chemotherapeutic effectiveness in man that it was possible to justify large-scale investigations by industrial and other research bodies. However, simultaneously with the introduction of laboratory brewing of penicillin on a major scale at Oxford, attempts were made to increase the yield by changes in composition of the medium and by selection of strains. These investigations gave no useful results at the time, though more extended studies on similar lines gave valuable results later in America.

For the laboratory large-scale production, there was a need for vessels more economical of incubator and steriliser space, and more convenient to handle, than the Erlenmeyer flasks initially used. Rectangular vessels with a side-arm were designed, and were specially constructed of porcelain (glass being at that time unobtainable). These vessels were designed to hold one litre of fluid in a layer about 1·7 cm. deep.

The raising of the scale of brewing immediately brought with it problems connected with extraction. Separating funnels were no longer adequate, and none of the laboratory counter-current extractors which had been described at that time was suitable, owing to the pH lability of penicillin and the formation of emulsion. After some unsuccessful attempts, a workable counter-current extraction apparatus was constructed, and this was used for more than a year before it was superseded. Difficulties of biological origin had also to be overcome: more than once the mould ceased to produce the active substances, and this was countered by paying particular attention to the inoculating cultures. A series of single spore isolations having been tested for yield of penicillin, a large number of subcultures of the most productive strain was made. As soon as these were well spored, they were stored in a refrigerator until required; from these, subcultures for sowing the vessels were obtained; later, master cultures of proved strains were preserved by lyophil drying. Then again, not infrequently the metabolism fluid was found to have lost its penicillin activity because of contamination by air organisms; some of these produce an enzyme (penicillinase) which destroys penicillin, and the consequent necessity for absolute sterility during the growth of the mould added enormously to the manufacturing difficulties. The months spent in increasing the output, with all their disappointments, frustrations and difficulties, are not likely to be forgotten by those involved. Undoubtedly the possibility that the drug might be of value in treating war injuries provided by this time a powerful stimulus to persevere.

The word 'penicillin' has been used in several senses. Originally, it referred to the broth in which the mould was grown; then it referred to the active substance in the broth; later it was applied to the material available for clinical use, and also to the pure substance. It is now known that the first dried extracts used at Oxford contained not more than 1 to 2 per cent. of the active substance, and the first material for clinical use contained about 5 per cent.; material containing 10 per cent. was considered unusually pure. This contrasts with the eventual use of virtually pure penicillin for clinical purposes. Although these relatively crude preparations had some minor disadvantages, they gave generally satisfactory therapeutic results, and it was indeed most fortunate that the impurities accompanying penicillin were so little toxic.

The product of the large-scale laboratory work was required for two purposes—for chemical investigations (see Chapter 9) and for trial in disease in man. All the early work was dominated by the struggle to accumulate even a few hundred milligrammes of the impure material for these purposes. Those who now use penicillin freely whenever they wish may find it difficult to believe that in the early years of the war the drug was so precious that even the traces remaining in test tubes and syringes were washed out and saved.

## EARLY CLINICAL TRIALS AT OXFORD

By the beginning of 1941, enough material and evidence had been collected to warrant a few trial injections in man. On January 27, 1941, the first patient to receive a parenteral injection of penicillin was given intravenously 100 mg. of material, 10 mg. of which had had no ill-effect on a 20-g. mouse. The patient, who was in the Radcliffe Infirmary, Oxford, was not suffering from any bacterial infection, but had an inoperable cancer. There was no reaction immediately after the injection, but three hours later there was a sharp rise of temperature with a rigor. Another injection, into a different patient, showed without doubt that the material was pyrogenic (i.e. capable of producing fever), a fact which was confirmed in rabbits. Fortunately, the pyrogenic agent proved not to be the same as the therapeutically active component, and it was possible by the use of chromatography to separate the two. When this difficulty had been overcome, enough material was collected to use on the first case of infection in man, routine pyrogen testing in rabbits being adopted for all material used for clinical purposes.

It was natural that the first cases made available for treatment should nearly all have been of the most severe type, in which all other possible treatments had failed. Though this selection was not governed by scientific considerations and entailed a severe test for the new drug, it had the advantage that the results were highly significant and easy to interpret. Five of the first six patients had dangerous staphylococcal or streptococcal infections which had not been controlled by surgical measures and sulphonamide therapy. The first, the treatment of whom was begun at the Radcliffe Infirmary on February 12, 1941, had a generalised staphylococcal infection with abscess formation and osteomyelitis. There was little idea at that time of how long treatment might need to be continued, and after five days, when considerable clinical improvement had been noted, the meagre stock of penicillin was exhausted; eventually the patient relapsed and died. The next patient, who was treated at the Wingfield-Morris Orthopaedic Hospital, was a boy with acute osteomyelitis due to a haemolytic streptococcus, which had not responded to other treatment. After penicillin had been given intravenously for five days the infection appeared to be completely controlled, but about four weeks later the patient relapsed. These first two cases are typical of those which received too little treatment. The struggle to make more penicillin was continued, and the later patients of the series were treated with greater success; the results confirmed the potentialities which the laboratory work had revealed. Several of the patients were children, who were chosen partly with the idea that less penicillin might be needed to treat them than to treat adults. A report on this series of cases, together with a detailed account of the methods of preparation, the pharmacological and the bacteriological properties

of penicillin, was published (Abraham, Gardner, Chain, Heatley, Fletcher, Jennings and Florey, 1941).

These early trials not only confirmed the opinion already reached that substantial doses of penicillin were not harmful to man, but gave a very good indication that even the most severe infections by pyogenic bacteria could be controlled. The effect on staphylococcal infections was especially important, as the sulphonamides were of relatively little value in these conditions. The results in some of the patients were so favourable that the work demanded further expansion, whatever the difficulties. Just how formidable an undertaking the preparation of penicillin was at that time, can be illustrated by the fact that one case of severe sepsis might need the brewing and processing of as much as 2,000 litres of medium.

## FURTHER EFFORTS TO INCREASE PRODUCTION

### WORK IN U.S.A. AND U.K.

It has already been indicated that, because of the war situation in Great Britain in 1941, the prospect of early commercial manufacture of any substantial amount of penicillin here was slight. Dr. Weaver, of the Natural Sciences Division of the Rockefeller Foundation, was accordingly approached with the suggestion that an attempt should be made in the U.S.A. to prepare larger quantities of penicillin for further clinical trials. As a result, Professor Florey and Dr. Heatley paid a visit to the United States in June of that year. They had discussions at the Northern Regional Research Laboratory, Peoria, of the U.S. Department of Agriculture, which were afterwards fruitful in the field of industrial production, and several American manufacturing firms were visited. Dr. Heatley worked first at Peoria and then with the firm of Merck & Co., Inc., imparting all the available information with a view to promoting the most rapid development of large-scale production. Tribute must be paid to the enterprise and energy with which the American manufacturing firms undertook production of the drug. Had it not been for their efforts, there certainly would not have been sufficient penicillin by 'D' day in 1944, to treat all severe casualties, both British and American, in the final campaign in Europe.

The fact that very little penicillin was available from either British or American manufacturing sources in 1941–2 spurred the Oxford workers to further efforts; brewing was increased, and a larger extraction apparatus of a different type was constructed. This depended on emulsifying the acidified brew with amyl acetate, and breaking the emulsion with a Sharples centrifuge. Help was in time received from Kemball, Bishop & Co., Ltd., who in September 1942, began to brew material in London and to bring the crude medium in 150 and 200 gallon lots (in milk churns) to Oxford, where it was put through the extraction plant. By the middle of 1942, small-scale commercial production by surface

culture methods was also being carried out by Imperial Chemical (Pharmaceuticals), Ltd., who supplied material for some of the clinical investigations.

## LATER CLINICAL TRIALS AT OXFORD AND ELSEWHERE IN BRITAIN

As soon as enough penicillin had been accumulated, a further series of clinical trials was started. These were carried out in the Radcliffe Infirmary, the Wingfield-Morris Hospital, the 101st General Hospital (Army) and the R.A.F. Hospital at Halton. An arbitrary dose of 1,000 units per lb. of bodyweight per twenty-four hours was found to be effective in several cases, but it was soon realised that a method for estimating the amount of the drug in the blood would be needed in order to control the size of the dose and ensure effective treatment. The cylinder-plate method, which was tried at first, was not sufficiently sensitive, so a simple slide dilution method, requiring only a drop of blood, was devised. The principle was always maintained that a concentration of penicillin which would demonstrably inhibit the infecting organism should be present in the blood as nearly continuously as possible. With the aid of the slide dilution test it was possible to formulate a basic dose and frequency of administration, which experience showed to be adequate for the treatment of the majority of penicillin-sensitive infections.

An account of this further series of clinical trials was published (Florey and Florey, 1943); it comprised 15 patients treated by general and 172 by local administration. Of the 15 patients with serious illnesses, 13 were given penicillin by intravenous or intramuscular injection, and all ten with severe staphylococcal infections recovered, as did also a patient with streptococcal meningitis. A patient with subacute bacterial endocarditis improved during treatment, but relapsed when the penicillin was stopped. Two patients with actinomycosis, to whom the dosage given was probably inadequate, yielded no definite information; and in one patient a streptothrix infection appeared to be eliminated. In the majority of the 172 patients with miscellaneous septic conditions treated by the local application of penicillin, staphylococci and streptococci were eliminated from the lesions and healing was rapid.

With the co-operation of Mr. R. G. Macbeth and Mr. G. H. Livingstone, a group of patients operated on for suppurative mastoiditis was treated by local instillation of penicillin through tubes, after complete suture of the wound. This method was later adopted with success in North Africa to treat war wounds. The adaptation of the usual methods of local treatment to the requirements of penicillin therapy was among the most interesting technical features of the clinical work, the object always being to keep the penicillin in contact

continuously with all infected parts. Thus, a chronic sinus, after penicillin had been inserted, was occluded with a rubber bung, and drainage tubes, even in septic wounds, were opened only at intervals to aspirate exudate and insert more penicillin. The same principle was subsequently extended to other fields of surgery.

### PENICILLIN TREATMENT OF WAR WOUNDS AND BURNS

Simultaneously with the work just described, the first attempts were made to control sepsis in burns with penicillin. Dr. Leonard Colebrook and his collaborators in the Medical Research Council Burns Unit at the Royal Infirmary, Glasgow, and Wing Commander D. C. Bodenham at the R.A.F. Hospital, Halton, were able to control streptococcal and, to a lesser extent, staphylococcal infections by local applications of penicillin supplied from Oxford. Bodenham (1943) was the first to dilute penicillin with sulphanilamide powder for local application.

The first use of penicillin in war wounds was initiated in April 1942, when a small quantity of penicillin, prepared in Oxford, was offered to the Director of Pathology, War Office, and was despatched to the Middle East. This material, which contained 30 to 40 units per milligramme, was used for local application to wounds which had long been suppurating (Pulvertaft, 1943). The results were encouraging, in spite of the difficult character of the cases.

The main attack on the treatment of war wounds with penicillin began early in 1943, when sufficient quantities were available from the laboratory at Oxford, Messrs. Kemball, Bishop & Co., Ltd., and Imperial Chemical (Pharmaceuticals), Ltd., to make it worth while for the Army to send special investigators to North Africa. For this purpose, Lt. Colonel Ian Fraser, a surgeon, and Major Scott Thomson, a bacteriologist, went to Algiers in May 1943, after preliminary training in penicillin techniques at Oxford. About three weeks later Professor Florey and, a month after that, Brigadier H. Cairns also went to North Africa, bringing further supplies of penicillin from the Therapeutic Research Corporation. In a confidential report presented to the War Office and the Medical Research Council in October 1943, it was stated:

> "It should be clearly understood that the object was not primarily to ascertain whether penicillin was capable of dealing with Gram-positive organisms in septic conditions; this we consider has been amply shown in England already. The main problem was to learn to employ the small quantities of penicillin likely to be available for service use to the best advantage. The work, then, has been designed to give an answer to the questions: can penicillin be used effectively in the field at all; and, if so, how much is required, and at what place in the Army organisation can it be used to the best advantage ?"

The first patients treated in this study all had chronic sepsis, of duration varying from a few weeks to many months. Preliminary trials

showed that superficial sepsis could be greatly benefited by local applications of penicillin and that parenteral administration offered hopes for the successful treatment also of deep-seated infections; unfortunately, however, owing to the extremely limited supplies of penicillin then available, very few patients could be given the drug parenterally. As a result of this work, it was realised (in the words of the report) 'that it was far too late to start penicillin treatment weeks or months after wounding, at a Rear Base hospital, and that its use should be tried much earlier, before the establishment of serious infection'.

Accordingly, a new scheme was devised for treating the expected casualties from the impending invasion of Sicily. It was arranged to receive them, as soon as possible after wounding, in Base Hospitals at Sousse and Tripoli, where penicillin therapy could be started with the minimum of delay. To implement this plan, the help of a number of experienced war surgeons and pathologists was obtained; they included, among others, Lt. Colonels J. S. Jeffrey, A. L. d'Abreu, E. L. Button, and D. W. Jolly, together with Majors K. C. Eden, H. L. de Waal, and W. E. Hamilton. The decision was made to close wounds by suture at first definitive operation performed at the Base hospital, relying on the local, and sometimes also parenteral, use of penicillin to suppress or abolish sepsis at that stage and to permit early healing.

Casualties were received at the Forward Base from two to twenty-two days after wounding: a few of the airborne and area troops had wounds of less than twelve hours' duration. Their previous treatment had usually included surgical excision, together with sulphonamide therapy (local and systemic). Nearly all the men, on arrival at the Forward Base, had wounds so infected that the surgeons concerned in this trial would not ordinarily have considered closure without further preparatory treatment.

The effect of the decision to combine immediate suture with penicillin therapy was that, of 171 soft tissue wounds, some of the most severe type, 104 healed completely, while in only seven did the suture line entirely break down. The results in compound fractures of the femur, treated parenterally with penicillin after suture, were less good, though those in compound fractures of other bones were encouraging. Some preliminary trials of penicillin in the treatment of head wounds were also made at this time.

Further developments of the work were possible in the Italian campaign, for which Lt. Colonel Jeffrey was appointed Penicillin Officer and Major Scott Thomson, Bacteriologist. Large numbers of cases were treated on the lines already formulated, and with increasing experience—and the widespread adoption of the 'two-stage' operation of wound closure—great improvements in the end-results both of soft tissue wounds and of compound fractures were recorded. Moreover,

penicillin therapy was used with good effect in the treatment of wounds of special types, such as those of the head and thorax.

By June 1944, when the invasion of Normandy started, the situation was entirely different from when the first trials were carried out on war casualties, in that there was sufficient penicillin to permit its systemic use on a very wide scale. The scheme of prophylactic injections of penicillin against wound infection in the severely injured, adopted at this time, and the remarkably good results obtained with it and subsequent applications of penicillin therapy in the final stages of the war, have been discussed in Chapter 3. Much of the success attending the use of penicillin for the treatment of the wounded is to be attributed to the high quality of the war surgery, and this again received a great stimulus because surgeons provided with penicillin were able to suture even the most severe wounds without the danger of major sepsis.

## THE WORK OF THE PENICILLIN CLINICAL TRIALS COMMITTEE

A Penicillin Clinical Trials Committee (Appendix I) was appointed by the Medical Research Council in March 1943. The situation leading to its formation was, briefly, as follows. The work at Oxford which has been described above had made it clear that penicillin was a chemotherapeutic agent of great importance, but while many of the potentialities of the new drug had been demonstrated, its promise in other directions remained to be explored. Such a task was beyond the capacity of any one institution or group of workers, and it was considered desirable to widen the field of clinical study. Although the commercial production of penicillin at last promised a substantial yield, supplies of the drug were still very limited; it was therefore necessary to arrange for the control of penicillin distribution by a responsible body which would ensure that the available stocks were used to the best advantage. The committee's function was to increase knowledge of penicillin therapy by developing improved technical methods of administration, and by extending the range of use of the drug to include conditions in which experience of its action was lacking; of the latter conditions, many were caused by bacteria known to be susceptible to the action of penicillin *in vitro*.

This was a difficult objective to reconcile with humanitarian claims, and for many months, owing to the extreme scarcity of penicillin, the committee, and those who tested the drug on the committee's behalf, were compelled to refuse treatment which might have proved beneficial to individual patients but would not have advanced knowledge of the drug's action. So grave was the shortage at that time, that there would not have been nearly enough penicillin to treat only the cases of staphylococcal septicaemia which came to the committee's notice; and, of all dangerous infectious diseases, this most imperatively demanded

penicillin treatment, since there was no satisfactory alternative. Both then, and later when the availability of increased supplies warranted a certain amount of routine treatment as well as research with the drug, the relative merits of its different uses—life-saving in septicaemia, reduction in the period of incapacity of fighting men with less serious infections, and the prevention of disablement following accidents to war-factory workers—repeatedly involved the gravest questions of principle and the most difficult decisions. The last such decision was taken as late as January 1945, when, despite the heavy expenditure of penicillin involved, it was determined to embark on the treatment of cases of subacute bacterial endocarditis. In the days of shortage there was complete agreement by all concerned that patients with war wounds should have priority in penicillin treatment.

The amount of penicillin initially available sufficed only to supply each of four centres in the United Kingdom with about 6,000,000 units of penicillin monthly. The centres were situated at the Radcliffe Infirmary, Oxford, and at St. Mary's, the Middlesex and St. Bartholomew's Hospitals, London. A further supply was allocated to the School of Pathology at Oxford for the continuation of research into the chemical constitution of penicillin (see Chapter 9).

As the existence and purpose of the committee became known, a great flow of requests for grants of penicillin for therapeutic purposes began. Although large numbers of these had to be refused, it was possible to accede to many which were accompanied by proposals for original and promising lines of study. Fortunately, the amounts of penicillin required were often small, and supplies steadily, though slowly, increased. Eventually, grants of penicillin for specific schemes of research were being made to 42 centres in the United Kingdom—general medicine and surgery (8 centres), orthopaedics (5 centres), neuro-surgery (5 centres), burns (9 centres), ophthalmic conditions (4 centres), chest injuries and diseases (3 centres), ear, nose and throat conditions (3 centres), puerperal septicaemia (1 centre), diseases of children (2 centres), venereal disease (2 centres) and bacterial endocarditis (14 centres). Some of these centres received as little penicillin as 100,000 units a month, and the total distribution of 100 million units a month represented but a fraction of what was at that time being used in America. The emphasis which had to be laid on economy was not wholly disadvantageous, however, since it encouraged attempts to use penicillin by the less extravagant method of direct local application rather than by systemic injection, and this field of use for the drug proved highly fruitful. In the treatment of battle casualties the British Army continued to use penicillin by local application in many types of wounds long after lease-lend penicillin had become plentiful; and the local application of penicillin in the treatment of diseases of the skin, in burns, in mouth infections, in infections of the serous cavities and

meninges, and in various other conditions, was largely developed in the research centres established by the committee. Reports from the various centres were submitted at regular intervals, and the committee arranged for their dissemination both in this country and abroad. Most of these reports were subsequently published in medical journals.

Almost the whole of the pioneer work on which the present knowledge of penicillin therapy is based was done in the United Kingdom and the United States. Although penicillin was a British discovery, U.S. workers had the advantage of enormously greater supplies of the drug in its early years; studies at many centres in America had begun months before anyone outside Oxford had handled penicillin in Great Britain, and American output reached a spectacular level while the British was little more than a scanty trickle. Only when American penicillin was placed at the free disposal of our fighting services was it possible for British clinicians to use it on an adequate scale. Nevertheless, some of the most substantial contributions to knowledge of penicillin therapy were made by British investigators in the days of scarcity.

An important part of this work was the treatment of a sufficient number of cases of infections known to respond to penicillin in order to define appropriate dosage, to improve methods of administration and laboratory control, and to observe the effect of various factors on the prognosis; in this way, it was possible to formulate optimum therapeutic policy. This was the main task of the four original centres, each of which also developed its own particular interests. At St. Mary's Hospital, London, Professor Sir Alexander Fleming and his colleagues made a thorough study of the effect of single and multiple doses, by various routes, on the penicillin content of the blood, and of micro-methods for determining the penicillin content of body fluids (Fleming, Young, Suchet and Rowe, 1944; Fleming, 1944); this centre also undertook the treatment of gonorrhoea and its complications. The researches at the Middlesex Hospital included observations on the treatment of pneumonia (Hudson, Meanock, McIntosh and Selbie, 1946); while at St. Bartholomew's Hospital the method of giving penicillin by intramuscular drip was explored (Morgan, Christie and Roxburgh, 1944), as was the use of penicillin locally in the treatment of skin infections (Barron, Christie, Fraser, Garrod *et al.*, 1944).

Several individual studies also call for special mention. A very important one was that initiated in North Africa in 1943 by Professor Florey and Brigadier Cairns, on methods of treating war wounds, to which reference has been made earlier in this chapter. A large proportion of the supplies of penicillin then available was devoted to this work.

Another important study was that of Brigadier Cairns and his colleagues on the penicillin treatment of septic meningitis (Cairns, Duthie, Lewin and Smith, 1944); the best ways of using the drug in these dangerous cases were carefully tested at the Hospital for Head

Injuries, Oxford. Clinicians receiving supplies of penicillin from the committee also contributed largely to defining the necessary conditions for success in the treatment of osteomyelitis (Hudson, 1946), and to determining the best methods of applying penicillin in the treatment of infections of the pleura and lung. The first centre for the penicillin treatment of syphilis in England was established at Liverpool (that the drug was of value in this infection had been shown earlier in America). The treatment of infections of the mouth and throat by means of penicillin pastilles was developed at one of the centres established by the committee in London (MacGregor and Long, 1944, 1945). Overseas, the value of penicillin in yaws and in tropical ulcer was demonstrated by Findlay, Hill and Macpherson (1944) and Hill, Findlay and Macpherson (1946), using penicillin allocated to the R.A.M.C. on the committee's recommendation.

As well as acting in an advisory capacity to the Ministry of Supply and the Ministry of Health on numerous problems relating to the production and distribution of penicillin in this country, the committee arranged for the training of surgeons and pathologists in the proper uses of the drug; it also had a major share in planning the arrangements for penicillin treatment of air-raid casualties and of the large number of battle casualties expected after 'D' day (see Chapter 3). The first step to these ends was the issue by the Medical Research Council of a memorandum on the use of penicillin in treating war wounds, which was prepared by the committee (Medical Research Council, 1944). On the basis of this memorandum and of subsequent work, courses in the clinical uses and laboratory control of penicillin therapy were provided at the three principal penicillin research centres in London. Surgeons and pathologists were selected by the Ministry of Health from the various regions in England, so that they in turn could pass on the information to those likely to be concerned with the treatment of war casualties. Between February and May 1944, 260 surgeons and pathologists received this course of instruction at the centres established at St. Mary's, the Middlesex and St. Bartholomew's Hospitals.

At the same time a sub-committee was appointed to advise the Emergency Medical Services on the equipment and organisation required for the penicillin treatment of battle casualties. This was no simple matter, since it had been decided that severely injured patients should receive three-hourly injections of the drug in ambulance trains, transit hospitals and at ports, as well as in base hospitals. This organisation, which was set up at short notice, worked efficiently, and most casualties who could benefit from penicillin received a regular series of injections starting at the Field Transfusion Unit and continuing throughout transit to the Base Hospital. Centres to investigate special problems bearing on the treatment of battle casualties with penicillin

were formed in three of the transit hospitals and in an airport hospital.

The final activity of the Penicillin Clinical Trials Committee was to organise an extensive investigation of the treatment of subacute bacterial endocarditis with penicillin. Fourteen centres in England, Wales, Scotland and Ireland took part in this co-ordinated study, and between February 1945 and February 1946, 201 cases were treated. A preliminary report on this investigation (Christie, 1946), showed clearly that while the scale of penicillin dosage appropriate to conditions other than subacute bacterial endocarditis was usually ineffective in that disease, the administration of larger doses for twenty-eight days or more could often cure it in its early stages. A much higher proportion of successes in treating subacute bacterial endocarditis has been obtained with the massive doses of penicillin which have become available since the end of the war (Christie, 1948, 1949; Cates and Christie, 1951), and this disease has now taken its place in the list of previously lethal infections in which treatment by penicillin and the newer antibiotics that have followed it has transformed the outlook.

## Publications relating to Chapter 7

### WAR-TIME RESEARCH ON THE SULPHONAMIDES

(NOTE: It will be realised that only a small selection from the enormous British output of war-time publications on the sulphonamide and sulphone drugs and related problems of chemotherapy is given here; the papers listed are mostly, but not exclusively, those referred to in the text of this chapter.)


ANDERSON, D. E. W. and CRUICKSHANK, R. with a note on the preparation of the drug, by WALKER, J.—
The treatment of bacillary (Flexner) dysentery with sulphanilylguanidine. *Brit. med. J.*, 1941, **ii**, 497.

BANKS, H. S.—
Sulphathiazole in cerebrospinal fever. *Lancet*, 1941, **i**, 104.
Meningococcosis: a protean disease. (Milroy Lecture.) Ibid., 1948, **ii**, 635, 677.

BULMER, E. and PRIEST, W. M.—
Bacillary dysentery: chemotherapy in its treatment. An experience of 492 cases in the Middle East. *Lancet*, 1943, **ii**, 69.

COLEBROOK, L.—
Treatment of war wounds by sulphonamide packs. *Lancet*, 1940, **ii**, 113.

COLEBROOK, L. and CAWSTON, W. C.—
Are the sulphonamides merely bacteriostatic agents? *Lancet*, 1945, **i**, 394.

DEPARTMENT OF HEALTH FOR SCOTLAND—
Sulphonamides in the treatment of meningococcal meningitis. Report of the Scientific Advisory Committee. Edinburgh: H.M. Stationery Office, 1944.

EVANS, D. G., FULLER, A. T. and WALKER, J.—
New drugs active in the chemotherapy of experimental gas gangrene. *Lancet*, 1944, **ii**, 523.

FAIRLEY, N. H. and BOYD, J. S. K.—
Dysentery in the Middle East, with special reference to sulphaguanidine treatment. *Trans. Roy. Soc. Trop. Med. Hyg.*, 1943, **36**, 253.

FILDES, P.—
A rational approach to research in chemotherapy. *Lancet*, 1940, **i**, 955.

FULLER, A. T.—
Rapid clinical method for the estimation of sulphanilamide. *Lancet*, 1942, **i**, 760.

FULLER, A. T., COLEBROOK, L. and MAXTED, W. R.—
The mode of action of sulphanilamide. *J. Path. Bact.*, 1940, **51**, 105.

FULLER, A. T., HAWKING, F. and PARTRIDGE, M. W.—
The rate of absorption of sulphonamides *in vitro* and *in vivo* after local application. *Quart. J. Pharm.*, 1942, **15**, 127.
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FULLER, A. T., TONKIN, I. M. and WALKER, J.—
Chemotherapeutic agents of the sulphone type. Part II. Sulphones related to benzamidine and benzylamine. *J. Chem. Soc.*, 1945, 633.
GOODWIN, L. G. and FINDLAY, G. M.—
Absorption and excretion of sulphonamides applied locally. Observations in rabbits. *Lancet*, 1941, **i**, 691.
GORDON, R. A. and BOWERS, V. H.—
Toxic blood-level of sulphanilamide from local application. *Lancet*, 1942, **ii**, 484.
GREEN, H. N. and BIELSCHOWSKY, F.—
The mode of action of sulphanilamide. II. The anti-sulphanilamide and other anti-bacteriostatic factors in bacterial extracts. *Brit. J. exp. Path.*, 1942, **23**, 1.
The mode of action of sulphanilamide. III. The relation of chemical structure to the bacteriostatic action of aromatic sulphur, selenium and tellurium compounds. Ibid., 1942, **23**, 13.
HARPER, G. J. and CAWSTON, W. C.—
The *in vitro* determination of the sulphonamide sensitivity of bacteria. *J. Path. Bact.*, 1945, **57**, 59.
HARRIES, G. E.—
Cerebrospinal fever: a review of 500 cases treated by chemotherapy without intrathecal serum. *Brit. med. J.*, 1942, **ii**, 423.
HAWKING, F.—
Local concentration of sulphonamide compounds inserted into wounds. *Lancet*, 1941, **i**, 786.
Prevention of gas-gangrene infections in experimental wounds by local application of sulphonamide compounds and by sera. *Brit. med. J.*, 1941, **i**, 263.
Blood concentrations following local application of sulphonamide compounds to wounds. Ibid., 1941, **i**, 511.
Methods for the local application of sulphanilamide. Ibid., 1941, **ii**, 685.
The rate of diffusion of sulphonamide compounds. *Quart. J. Pharm.*, 1941, **14**, 226.
Effect of sulphonamide preparations on experimental infected wounds. *Lancet*, 1942, **ii**, 507.
The local action of sulphonamides. *Practitioner*, 1943, **151**, 354.
Recent work on the pharmacology of sulphonamides. *Brit. med. J.*, 1945, **i**, 505.
HENDERSON, D. W. and GORER, P. A.—
Treatment of certain experimental anaerobic infections with sulphapyridine and with immune sera, and the problem of synergic action. *J. Hyg., Camb.*, 1940, **40**, 345.
JOE, A.—
Treatment of cerebrospinal fever by sulphapyridine. (Honyman Gillespie Lecture.) *Edinb. med. J.*, 1942, **49**, 628.
MACARTNEY, D. W., SMITH, G. S., LUXTON, R. W., RAMSAY, W. A. and GOLDMAN, J.—
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MCILWAIN, H.—
Amino-sulphonic acid analogues of natural amino-carboxylic acids. *J. Chem. Soc.*, 1941, 75.
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# CHAPTER 8

# INDUSTRIAL HEALTH RESEARCH

DURING the period between the First and Second World Wars, the Medical Research Council promoted a number of important investigations on problems affecting the health and well-being of workers in industry, through the medium of the Industrial Health Research Board and of various special committees. The Board had assumed the functions originally performed by the Health of Munition Workers Committee, which had been set up during the First World War; that committee's terms of reference were to consider and advise on industrial fatigue, hours of labour and other matters affecting the health and efficiency of workers in munition factories and workshops. In its final report it urged that arrangements be made without delay for a national scheme of industrial medical research, and that fuller recognition be given to the importance of industrial hygiene. It was dissolved in 1917, and shortly afterwards the Medical Research Committee (now the Medical Research Council) and the Department of Scientific and Industrial Research jointly appointed the Industrial Fatigue Research Board. This subsequently became part of the organisation of the Medical Research Council and was renamed the Industrial Health Research Board.

By the time of the outbreak of war in 1939 a mass of scientific data on various problems of industrial physiology, psychology and toxicology had been collected and analysed by the Board and associated expert committees of the Council; the results of most of the studies had been published in a series of special reports issued under the Board's authority, and many of the recommendations had been implemented by industry. Extensions of these studies to war-time conditions, and a great increase in the programme of work in industrial medicine and toxicology promoted by the Medical Research Council, constituted the main British contributions to industrial health research during the war, but important work on the health hazards in particular industries was carried out also by the members of the staffs of certain government departments, notably the Ministry of Supply and the Factory Department of the Ministry of Labour and National Service.

Early in 1940, the Medical Research Council issued in pamphlet form a summary of the chief findings of the Industrial Health Research Board and its predecessor, the Health of Munition Workers Committee, which were capable of immediate application in furtherance of the national effort (Industrial Health Research Board, 1940); this contained recommendations in respect of hours of work, observance of regular

rest periods, problems of lighting and vision, heating and ventilation, the prevention of accidents, and the reduction of sickness absence and labour wastage. However, the lessons learnt in 1914–18 regarding the deleterious effects of excessively long hours of work on health and output were soon forgotten under the even greater stresses of the Second World War, as was exemplified by events in industry during the months following the evacuation from Dunkirk. At that time there was an insistent demand for more and more munitions and equipment to replace those lost upon the Continent and to prepare for the next stage of the conflict. The response of management and workers was equal to the urgency of the situation, and for many weeks both men and women in war factories endured excessively long working hours without holidays or respite. The inevitable result was that although the output at first reached an exceptionally high level, this could not be maintained: and the ill-effects of the almost superhuman effort put forth were eventually reflected in an increased amount of sickness absence. These facts were clearly established in a series of surveys carried out under the Board's authority. The results were published in a memorandum (Industrial Health Research Board, 1942), which recommended that, over an extended period, the weekly hours of work should generally not exceed 60 to 65 for men and 55 to 60 for women. Stress was laid on the importance of the week-end rest break, and on the value of the newly introduced system of staggered holidays. The lower figures for weekly working hours suggested were subsequently accepted by Government as the maxima compatible with continued health and working efficiency and with sustained output over a long period.

The programme sponsored by the Board from its inception until 1939 had related chiefly to physiological, psychological and environmental factors affecting a normal industrial population. The coming of war-time conditions brought out a number of new problems, including the need to employ vast numbers of women, of inexperienced new workers, and of workers from the older age groups. Many of the resultant human problems were investigated by Dr. S. Wyatt and his colleagues, as members of the staff of the Medical Research Council working for the Board; some of their studies are discussed in the next four paragraphs.

In the latter months of 1940 there was much uninformed criticism of the amount of absenteeism, particularly among women, in industry. A statistical survey was therefore undertaken of the extent and distribution of 'absence' in random samples of women workers in two Royal Ordnance Factories over a period of six weeks (Wyatt, Marriott and Hughes, 1943). It was found that very few women were habitually absent for one or two shifts in each week, and that the great majority of the absentees were away for periods of varying length at irregular

intervals. Thus, whatever the main causes of absence from work, they were not regularly recurrent, but were as varied as individual needs and circumstances. This suggested a need for study of the personal causes of absence, and for an individual method of dealing with them—a policy which was subsequently adopted in industry with increasing success.

In the latter part of 1942, a further reduction in the weekly hours of work was made in a number of factories engaged on war production. The results of an investigation on groups of workers in different factories showed that, in the few instances where it was possible to separate the effects of shorter hours from those of other conditions, the reduced working hours had resulted in a small but definite improvement in hourly output. In most of the factory groups, however, any relationship between hours and output was obscured by the much greater influence exerted by changes in the type or design of product manufactured, mechanical difficulties, variations in the quantity and quality of the materials used, progressive improvements in the methods or conditions of work, changes in the type or lay-out of machines, and by personal factors such as dissatisfaction with the method or rate of payment. The inquiry provided some indication of the relative importance of these different factors for both the work and the workers.

In 1942–3, a survey was made of the amount, distribution and nature of certified sickness absence in some 20,000 women industrial workers (Wyatt *et al.*, 1945). The absence rate was found to be highest in the age-group 30–50, and the amount of sickness absence of married women exceeded that of single women by 65 per cent. This much greater incidence of sickness absence among the married women was attributable not only to the extra effort in running a home, but also to anxiety for husbands and sons on war service, and to the break-up of family life so commonly caused by the war. Functional nervous disorders ranked high among the causes of sickness absence. The investigation incidentally showed the great value of complete and accurate records of sickness absence as an index of industrial health.

This statistical study was followed by an inquiry into the predisposing causes of ill-health among women in industry, in which groups of women with high and low incidence of sickness absence, respectively, were interviewed in order to ascertain their personal attitudes towards various factors both inside and outside the factory (Wyatt *et al.*, 1945). Among the many points brought out was the widespread, though not universal, unpopularity of night-work. Only about one-third of the women interviewed liked working at night; about 40 per cent. of those on night-work spent not more than six hours of the twenty-four at rest in bed, and there was other evidence that night-work imposed extra physical and mental strain, largely owing to the dislocation of normal eating and sleeping habits.

Since satisfactory study of trends of sickness within an industry, or for the comparison of factory with factory or trade with trade, depends on an efficient method of recording sickness absence, a special committee of the Industrial Health Research Board was appointed to study the matter. A preliminary report of the findings of this committee was published in 1944.

One important new development during the Second World War was the widespread application of methods of research in industrial physiology and psychology to the human problems of the Fighting Services (see Chapter 2), and, conversely, the realisation that the techniques and results of researches undertaken initially for one or other of the Services might be applicable also to industrial problems. Several members of the staff of the Medical Research Council, who had previously been engaged on industrial studies for the Board, worked mainly or partly for the Service Departments or the Personnel Research Committees during the war years, their special experience of applied psychology or environmental physiology lending itself equally to studies of the human factor in industry and of the reactions of the sailor, soldier or aviator to the exigencies and stresses of his task.

Reference has been made in Chapter 2 to the setting up by the Medical Research Council of a Research Unit in Applied Psychology in the Psychological Laboratory at Cambridge; although the work of the Laboratory and the Unit during the war years was concerned mainly with Service problems, a number of matters of direct importance to industry were also investigated. Another major development during the war was the substantial increase in the Council's programme of work on occupational hazards and diseases, mentioned at the beginning of this chapter. Various problems of industrial disease, such as lung disease in coalminers and cotton spinners, miners' nystagmus, and the toxicity of industrial solvents, had earlier been the subjects of special studies, but the war brought into prominence a number of other industrial hazards demanding urgent attention. The Industrial Health Research Board was reconstituted from this point of view in 1942, and a Department for Research in Industrial Medicine, under Dr. Donald Hunter, was established at the London Hospital in 1943, while at different stages of the war, special units were set up at Birmingham, Glasgow, Newcastle and Sheffield for research on wound infection, burns and scalds, and traumatic shock, all of which presented problems with an important bearing on industrial injuries. Developments at the end of the war period included the formation of a Pneumoconiosis Research Unit at Cardiff, to extend the earlier work on lung diseases in coalminers, and to study questions of rehabilitation for the men affected; and the reconstitution of the Wound Infection Unit at Birmingham into a Research Unit in Industrial Medicine, with special reference to occupational skin diseases.

ENVIRONMENTAL FACTORS IN INDUSTRY

(i) *Ventilation and Air Hygiene.* The ventilation of air-raid shelters, factories and other buildings under war conditions presented urgent problems, which were often accentuated by the requirements of the 'black-out'; special difficulties in respect of ventilation and air hygiene arose in factories where noxious fumes or dusts were liable to accumulate. From 1940 onwards a Group for Research in Industrial Physiology at the London School of Hygiene under Dr. T. Bedford carried out observations on the ventilation of public and other air-raid shelters, at the request of the authorities concerned, and advised on measures for their improvement. Special investigations were made on atmospheric pollution in Royal Ordnance Factories, in relation to the risks of T.N.T. and tetryl poisoning. The atmospheric content of T.N.T. under different conditions was determined, and a figure was suggested for the maximum safe concentration of T.N.T. in the air. Specially high levels were noted at night under 'black-out' conditions, and measures had to be devised to deal with this problem. It was found possible to introduce improvements in ventilation and in filling methods which greatly enhanced the comfort and probably the efficiency of the workers, and reduced the risks of poisoning. Indeed, the fatality rate from T.N.T. poisoning was considerably lower in the Second than in the First World War. Similar work was carried out for the Air Ministry and Ministry of Labour on the ventilation of aircraft factories, especially in aircraft 'doping rooms'.

Closely related to the studies undertaken on ventilation problems was the work on airborne infection and air purification carried out as part of the war-time programme of the National Institute for Medical Research. Mention must also be made here of the work of Colebrook and others upon the treatment of burns and upon the control of wound infection, for the techniques they evolved became increasingly applied in industrial medical practice.

(ii) *Measurement of Environmental Warmth.* It was found during the war that the methods commonly used for the measurement of environmental warmth were not fully adequate under conditions of very high temperature, when radiation from hot surfaces was also high. Such conditions were frequently experienced in H.M. ships in the tropics, in ships' boiler rooms and in foundries. An investigation of this subject on behalf of the Royal Naval Personnel Research Committee (Chapter 2) introduced a method of measurement which made a reasonable allowance for radiant heat (Bedford, 1946).

(iii) *Industrial Lighting.* The problems of natural and artificial lighting of factories and offices under war conditions, including those imposed by the 'black-out', were studied by H. C. Weston, of the staff of the Medical Research Council, in a series of investigations of which the results had a direct bearing on the drafting of the Factories

(Standards of Lighting) Regulations, 1941. No standards of lighting had been defined under the Factories Act of 1937, and it was considered that the standards must be more generous in war than in peace, and that a higher standard should be prescribed for continuous fine work. It was recognised that artificial light sources would be more acceptable if rendered unobtrusive, and as far as possible simulated the effect of daylight. For this purpose, the tubular fluorescent lamp proved to be the most suitable. Other work included studies on the minimum standards of illumination permissible, in view of the need to economise in the use of electricity.

(iv) *Artificial Sunlight.* It had been assumed in certain quarters that ultra-violet irradiation would have a beneficial effect in compensating to some extent for the more objectionable features of the 'black-out', and a number of industrial undertakings introduced solaria for treating their employees by exposure to the rays of quartz mercury lamps for short periods weekly. It became a matter of both practical and scientific importance to determine whether such treatment did in fact exert the beneficial effects attributed to it. Under the auspices of the Industrial Health Research Board, a carefully controlled investigation was carried out in 1944–5 by Dr. Dora Colebrook on some 3,000 volunteers, in a Government office, a factory and a coalmine. Statistical analysis of groups of volunteers treated with short and long rays showed no differences between these groups in respect of sickness, duration of colds or, as regards the mining community, of total absence. About one third of the subjects treated in each group stated that their health had been better during the period of attendance at the clinic. There was no evidence that the reported benefit was due to the shorter rays.

Comparative analysis of treated and untreated groups of clerical and factory workers showed that the former fared no better than the latter in respect of sickness absence. In respect of colds, indeed, there was a significant advantage in favour of the untreated subjects, though this may have been due to difficulties in recording the experiences of the latter group. Both groups of the treated miners, i.e. those receiving and those not receiving the shorter ultra-violet rays, had a significant advantage over the untreated controls in that they had less sickness and total absence. Evidence was forthcoming, however, that the previous health of this untreated group, which could not be formed by random selection, was not so good as that of the treated men during the previous year. The general conclusion was that no evidence had been adduced that treatment by artificial sunlight was of benefit in decreasing sickness absence, or in lessening the severity of colds and other ailments. In regard to any subjective or psychological benefit from the treatment, the opinions of the volunteers were by no means unanimous (Colebrook, D., 1946).

## INDUSTRIAL PSYCHOLOGY

The field studies in industrial psychology made by Dr. S. Wyatt and his colleagues have been mentioned in the introductory section of this chapter. Work on other aspects of the subject is described below.

*Selection of Personnel.* The application of psychological methods in personnel selection both for the Fighting Services and for industry were developed and assessed by experts working on behalf of the Industrial Health Research Board in the Psychological Laboratory at Cambridge. Researches on selection problems for particular tasks in industry were directed principally by Miss A. W. Heim. Experiments were carried out at certain labour training centres, and a series of investigations was made in a number of factories engaged upon war work: not only was the technique of large-scale intelligence testing much developed, but some of its difficulties were more fully appreciated than hitherto. A noteworthy degree of success was achieved in determining aptitudes for the practical operations of machine manipulation, and for general inspection work. Preliminary studies were also undertaken on the validation of selection methods for foremen. In addition to intelligence tests, various others, such as 'inspection tests', 'manual dexterity tests' and 'alignment tests' were used as occasion demanded. A series of tests was also devised to help in job selection for the blind (Farmer, 1945, 1946).

*Accidents and Accident Prevention.* Much work on the problem of preventing industrial accidents, particularly by identifying the 'accident-prone' and excluding them from dangerous tasks, had been carried out for the Industrial Health Research Board by E. Farmer and his colleagues at Cambridge before the war (Farmer and Chambers, 1940). A memorandum embodying the results of these studies, together with an account of some of the environmental and other factors predisposing industrial workers to accident, was published in the Board's series of emergency reports (Industrial Health Research Board, 1942). It was difficult, during the war period, to secure conditions for adequately controlled experiment or for the collection of the necessary statistics for analysis. During the latter part of the war, however, J. W. Whitfield, working by statistical means, introduced a number of new methods, notably for the study of certain types of mining accidents.

*Neurosis in Industry.* In the early years of the war evidence from many sources indicated that neurotic illness was responsible for a considerable amount of sickness absence. Moreover, it seemed probable at that time that the incidence of neurosis would increase as the war progressed, both absolutely and in proportion to other causes of disability, until it became a serious threat to industrial efficiency. The extent to which this had already happened was unknown: no adequately controlled survey had been carried out, either for the population as a whole or for any section of industry. Existing factory records were of but little assistance in distinguishing psychological from physical illness.

Accordingly, in December 1942, the Industrial Health Research Board initiated an inquiry to determine the true incidence of neurosis among factory workers, to assess its effects on production and to examine the factors predisposing to it. The light and medium engineering industries were selected as the field for the survey, which was carried out under the direction of Dr. Russell Fraser on samples of workers in a number of factories situated mostly in and around Birmingham. Later the work was extended by the setting up of a second team in the Greater London area, under the direction of Dr. Elizabeth Bunbury.

The range of illness accepted as being covered by the term 'neurosis', the precautions taken to ensure the accuracy of diagnosis within the prescribed definition, and the reliability of the sampling procedure, all affect the validity of such a study. 'Definite neurosis' was defined as including only those disorders which were clearly illnesses both in the doctor's and in the patient's opinion, and which were clearly neurotic in nature and also disabling. Psychosomatic illnesses and neurotic disorders of less degree were included under the term 'minor neurosis'. Besides undergoing intelligence tests and having an interview by a social worker, and a full psychiatric assessment by one of the three physicians taking part in the survey, each individual was subjected to a number of special investigations, and a full physical examination where necessary. Over 3,000 men and women, representing a random sample from a total population of 30,000 workers employed in 13 factories, were interviewed and examined. In addition to information about neurosis, comparable data relating to the incidence of physical illness and its variation with environmental and constitutional predisposing factors were obtained.

The main findings of the survey (Fraser *et al.*, 1947) afforded striking confirmation of the importance of psychological factors in determining industrial efficiency. Over 25 per cent. of all sickness absence was due to neurosis, and 10 per cent. of the workers had suffered from disabling neurosis during the six months' period under review; a further 20 per cent. had suffered in a minor degree from similar disorders. Of the large number of possible determining factors whose importance was assessed, certain features in the constitutional make-up and environmental experience of the individual were shown to be most closely correlated with a high incidence of neurosis.

In the factories studied, neurotic manifestations were as frequent among those on the more skilled as among those on the less skilled jobs, and as prevalent among those usually receiving the highest earnings as among the less highly paid. The type of house and district in which the individual lived did not bear a significant relationship to the amount of illness experienced. Workers who had considerable domestic responsibility without excessive hours of duty showed less than the average

amount of neurosis; the same was true of those with a wide range of human contacts. A decrease in social contacts was the factor most commonly associated with neurotic disorder. Those whose leisure was spent alone, or with their immediate family only, suffered more than the average. To a lesser degree this was also the case with those lacking in recreation and leisure interests. Neurosis was more frequent among groups whose domestic circumstances were unsatisfactory, for example, those widowed or separated, and among married women with partial home duties (i.e. either housework or the care of children, but not both). This latter group of married women included most of those whose homes had been disrupted by the war. On the other hand, the married women with full home duties (including the care of children) enjoyed better health than the other married women, and as good health as the single women, though they had been more frequently absent from work. It became evident that war-time factory hours were unsuitable for married women with full home duties, but that with shortened hours such women could be efficient and healthy factory workers.

As might be expected, there were also indications that fatigue could contribute to the development of neurosis. Those whose diet had been least adequate had also suffered more, possibly because, among other factors, they had smaller resistance to the prevailing causes of fatigue. The nature of the worker's job, that is to say, whether it was congenial or boring, was also found to be relevant to the incidence of neurosis, and it was evident that many other aspects of the working environment might play a part; thus, poor lighting, which tends to make the task a strain and its environment gloomy, was associated with an increase of neurotic disorder. Further, not only are unsatisfactory human relationships outside the factory associated with a high incidence of neurosis, but the human relations within a factory are known to have an important influence on output, and, in the authors' view, they are likely to have at least an equal influence on the health of the worker.

### INDUSTRIAL DISEASES

*Lung Diseases in Coalminers.* In 1937, the Medical Research Council had organised a large-scale investigation into the incidence, causes and prevention of lung disease due to dust in the South Wales coalmines. The researches, which included clinical, radiological, pathological, physical, geological and chemical studies, were directed and co-ordinated by a special Committee on Industrial Pulmonary Disease. The problem was urgent, as the numbers of miners certified as suffering from silicosis had been increasing yearly, particularly in the anthracite area. Moreover, it was believed locally that other disabling pulmonary conditions besides those recognised as true silicosis were being caused by mine dust. The medical survey had shown that pulmonary

abnormalities extended throughout this coalfield, but that the incidence and severity were highest in long-term anthracite colliers. A relationship was found between the incidence of pulmonary abnormality among the colliers, as judged by X-ray evidence, and the 'rank' of the coal mined at the different collieries, though within the anthracite area there were also local variations in incidence. Further, the medical survey and pathological studies confirmed the local belief in a disability other than true silicosis, by bringing to light and defining another widespread pulmonary condition due to dust inhalation, which was termed 'dust-reticulation.' The environmental survey and experimental studies established that the primary factor responsible for the various pulmonary abnormalities was the airborne dust, and this factor was analysed further. Information was also provided about the strata most likely to be the source of danger, and about atmospheric conditions in the mines and the various methods of working. These studies suggested that differences between the hazards in the different mines were a function both of the quantity of the dust and of its physical and chemical nature. Current opinion in the United States of America tended to view the concentration of airborne quartz as the prime determinant of the incidence of pulmonary disease. The investigations in South Wales, whilst likewise incriminating quartz, indicated that other constituents of the dust, both coals and other minerals, might also be of decisive importance through enhancing, reducing or modifying the noxious action of the quartz. Legislation was subsequently provided to broaden the compensation allowed to coalminers, so as to include under the title 'pneumoconiosis of coalminers' the condition described as 'dust-reticulation', as well as the pulmonary abnormalities previously recognised. Powers were also granted to enable various new methods of dust suppression to be compulsorily introduced where deemed necessary, such as water infusion of the coal-face before working it, and sprays used in connexion with mechanical coal-cutters. Many fundamental questions, however, remained unanswered, and the problem of preventing pneumoconiosis in coalworkers was only partly solved.

Three special reports on different aspects of these studies were issued by the Medical Research Council during the war (Hart *et al.*, 1942; Bedford *et al.*, 1943; King *et al.*, 1945).

*Other Dust Diseases.* In iron foundries, workers are exposed to iron oxide, which produces changes in the lungs indistinguishable from silicosis, as well as to silicates and quartz. A large-scale investigation, involving the X-raying of over 2,000 workers, was undertaken to determine the incidence of silicosis and other pulmonary abnormalities due to dust in iron and steel foundries. It was shown that in the steel foundry workers the incidence both of silicosis and of other radiological abnormalities due to dust was approximately twice as high as that noted in men working in iron foundries. It was not, however, possible

to determine the exact nature of the responsible dust. Similar studies, but on a smaller scale, were carried out on workers in iron turneries, where some radiological evidence of dust reticulation due to iron oxide was discovered, though the workers had no noteworthy symptoms (Buckell, Garrad *et al.*, 1946).

Harding and others (1944) studied in detail the case of a man who had contracted pneumoconiosis while employed as a boiler scaler. In the following year McLaughlin and others noted the effect of silver and iron oxide($Fe_2O_3$) dust on the lungs of silver finishers. The latter, who use rouge in their work, were found to develop radiological abnormalities without suffering any disability, for neither the silver nor the iron oxide caused fibrosis of the lungs. Barrie and Harding (1947) reported further cases of the same kind and introduced the term 'argyro-siderosis' to describe the condition.

Investigations, carried out before the war, into the potential hazards from aluminium and alumina dusts in factories had revealed no evidence of deleterious effects on the workers. Further research on this subject was, however, rendered desirable by the apparently contradictory fact that, while observers in Canada had reported favourably on the value of aluminium dusts for the prevention and treatment of silicosis, reports from Germany alleged that an acute pneumoconiosis was common amongst those manufacturing aluminium powder. Studies were therefore undertaken by members of the Department for Research in Industrial Medicine at the London Hospital on the effects of aluminium and alumina dusts on persons whose task was to grind 'duralumin' aircraft propellers with wheels of calcined alumina. X-ray investigations, and analysis of the previous year's illnesses of a number of workers exposed to the dusts, disclosed no ill-effects which could be related to this occupation (Hunter *et al.*, 1944).

A special type of respiratory disease studied was that due to 'bagasse' dust. Bagasse, the dried sugar-cane fibre from which the sugar has been extracted, was imported from Louisiana in large quantities during the war for the manufacture of thermal and acoustic insulating board. The tightly-packed bales, as brought by ship to Great Britain, had usually to be broken open and shredded under 'black-out' conditions, at a time when, as a sequel to enemy air attacks, there was insufficient water available for damping down the dust. Under such conditions the dust constituted a serious hazard, and as many as 10 out of 21 men engaged in handling bagasse for more than three days during a period of 15 months developed bronchiolitis and pneumonia. In most cases the onset of the illness occurred some eight weeks after starting work on the shredding machines. In the series reported (Hunter and Perry, 1946) two patients died but the remainder recovered completely within six weeks. The exact aetiological agent in this disease could not be discovered.

To assist in the investigations undertaken into the risk of dust inhalation in various occupations, comparative tests of dust sampling instruments were carried out at the London School of Hygiene. As the result of studies of the dust hazard in coalmines, the thermal precipitator had been recommended as the standard dust sampling instrument. It was thought desirable, however, to investigate the efficiency of other types of sampler, and basic research had first to be undertaken upon the sedimentation of spherical and non-spherical particles (Davies, 1947), and upon light extinction methods of dust measurement. Methods were then developed for setting up clouds of spheres of approximately uniform size for the testing of sampling apparatus.

## INDUSTRIAL TOXICOLOGY

The manufacture of certain explosives and other substances used for military purposes involves risks of industrial poisoning, many of which were already known. These risks were sometimes accentuated by environmental conditions directly connected with the war; for example, the need for a strict 'black-out' often made proper factory ventilation difficult. During the war many materials new to industry were used on a large scale, before their possible effects on health had been explored.

Much research on known and potential health hazards due to toxic agents was sponsored by the Medical Research Council during the war years. Some of the numerous studies undertaken by the Department for Research in Industrial Medicine at the London Hospital related to hazards previously encountered in other countries, but which had not yet appeared in Great Britain, such as fluorosis due to the use of fluorides in aluminium factories.

*Radioactive Substances.* As research in the field of nuclear physics increased, so was careful medical supervision of the workers exposed to radiation instituted, and detailed records were kept of its effects.

Research was done under Professor S. Russ, of the Middlesex Hospital, on the degree of absorption into the body of radioactive substances used in the luminising industry (Jones and Day, 1945). Such were the precautions taken in the industry as a result of the experiences of the nineteen twenties, that .poisoning by luminising substances was unknown in this war.

*Poisonous Metals and their Salts.* In precious metal refineries examples occurred of poisoning with complex salts of platinum; the effects were a transient though recurrent syndrome of running of the nose, sneezing, tightness of the chest, shortness of breath and coughing (Hunter, Milton and Perry, 1945). Osmium tetroxide fumes, producing bronchitis and transient blurring of vision, were also investigated, and appropriate precautions were recommended (McLaughlin *et al.*, 1946). The hazard of chronic mercury poisoning was studied in a thermometer

workshop and in chemical works; many of the thermometer workers were found to be suffering from mild mercurialism, and it was suggested that this was due, at least in part, to absorption of the metal through the skin or by ingestion (Buckell, Hunter *et al.*, 1946).

*Fluorides.* An investigation was carried out in a works in Scotland in which aluminium was produced by an electrolytic reduction process requiring the use of fluoride fluxes (Agate *et al.*, 1949). A risk of fluorosis there had been indicated by the observation that cattle and sheep which had eaten grass contaminated with fluoride dust from the factory were in poor condition and had dental deformities. The occurrence of fluorosis in the sheep and cattle was confirmed, and clinical, radiographic and biochemical studies were made to determine the incidence and possible effects of fluorosis in workers at the factory and in people living in the neighbourhood.

The conclusion of this investigation was that, though a small number of the factory workers showed X-ray changes recognisable as those of the lesser degrees of fluorosis, the health of none of them was materially affected. People living nearby were not affected in any way. Nevertheless, there was undoubted evidence of fluorosis in domestic animals grazed round about the factory, and the ground was found to be contaminated for a distance of up to six miles away. A similar investigation (Bowler *et al.*, 1947) was carried out in a magnesium foundry in which fluoride fluxes were used to minimise the risks of fire.

*Inorganic Compounds of Arsenic.* Professor A. Bradford Hill and Dr. E. Lewis-Faning made a statistical study of the mortality experience, over 34 years, of factory workers in a certain area. This showed an unusually high incidence of deaths due to cancer, which might be attributed to working in a factory where arsenic was handled. Chemical process workers, engineers and packers in this factory had been especially affected, and the cancers from which they suffered had occurred most often in the lungs and skin. These observations were reported simultaneously with clinical and environmental investigations in the factory, which were made by Dr. K. M. A. Perry and others (Hill *et al.*, 1948).

*Trinitrotoluene.* Changes in the blood of a group of men and women university students who worked in an explosives factory were studied (Stewart *et al.*, 1945). They were under conditions where exposure to T.N.T. was heavy. A mild haemolytic anaemia developed in the majority, especially the men, particularly where the temperature and the concentration of T.N.T. were highest. The bone marrow was shown to respond by increased activity.

Laboratory studies and animal experiments undertaken elsewhere demonstrated that T.N.T. undergoes both oxidation and reduction in the body (Channon, Mills and Williams, 1944 ; Lemberg and Callaghan, 1944). Four reduction products were isolated and identified in the urine:

these were various dinitro-aminotoluenes, at least one of which, a hydroxyl-aminotoluene, was a powerful producer of methaemoglobin and might be responsible for the toxic effects of T.N.T.

Himsworth and Glynn (1942) found that T.N.T. could produce delayed liver damage in animals receiving a low-protein high-fat diet: it appeared to raise the metabolic rate and the need for protein.

*Tetryl.* Because of the frequency, in certain ordnance factories, of dermatitis due to tetryl, an investigation of the sensitising properties of this compound was undertaken at the National Institute for Medical Research (Gell, 1944). It was shown that tetryl reacted readily with amino-groups (and therefore with proteins) to form *N*-trinitrophenyl (or 'picryl') derivatives with specific immunological properties.

*Organic Solvents.* Workers in Oxford were concerned with chronic carbon tetrachloride intoxication in the chemical industry (Stewart and Witts, 1944). They found certain symptoms such as mental hebetude, and gastro-intestinal disturbances due to hypermotility of the stomach and intestine, which had previously been ignored or confused with the manifestations of acute poisoning. These were causing serious loss of working time. There was reason to think that they were due to action of this solvent on the central nervous system.

Trichlorethylene and other substances used in industry were also examined, and their absorption, elimination and metabolism were studied (Powell, 1945).

*Phosphine.* The risk from phosphide dust and gaseous phosphine during the process of manufacturing life-saving flares was investigated, and some cases of transient poisoning were observed. No evidence of any persistent damage to the blood-forming system was found, and it was considered probable that previous findings of its occurrence might have been due to the presence of arsine as a contaminant of the phosphine.

*Other Industrial Poisons.* Among other investigations carried out upon industrial poisons were studies of the risk of benzene intoxication in workers using aeroplane dope and industrial rubber solvents, but no intoxication was discovered and the factory atmospheres were found not to contain toxic quantities of these solvents. The skin damage that can result from methyl bromide, which has been used extensively as an insecticide and as a fire extinguisher, was also investigated (Butler *et al.*, 1945). A few cases of acute toxic polyneuritis occurring amongst workers making tri*ortho*cresyl phosphate for use as a plasticiser were discovered; in this last instance the method of entry of the poison into the body was almost certainly by absorption through the skin (Hunter *et al.*, 1944).

## THE EFFECTS OF VIBRATION

The effects produced by the vibration of pneumatic drills and similar appliances on the hands of the operators were studied at the

London Hospital. The prolonged use of vibrating tools driven by compressed air or electricity, and the operations involved in grinding metal castings against large grinding wheels, were found to produce vascular disturbances of the hands; these were manifested as the transient local pallor, insensitivity and stiffness of the fingers in response to cold, known as Raynaud's phenomenon (Agate, Druett and Tombleson, 1946). The same condition was investigated in a group of pneumatic tool workers, including rivetters, caulkers, fettlers and others, and the vascular phenomena were found to be of frequent occurrence (Hunter, McLaughlin and Perry, 1945). Occasionally these changes were so severe as to prevent men from continuing their occupation. The syndrome usually developed after two to five years of such work. The joints of the workers were X-rayed, since observers in Germany had reported that arthritis was liable to follow the use of vibrating tools; arthritic changes however, were, found to be relatively rare. Further studies resulted in the development of an accurate instantaneous electronic method for recording and analysing the vibrations produced by a tool while in operation (Agate and Druett, 1946). This method enabled detailed studies of many tools and processes to be carried out, and some of the common physical characteristics of harmful vibrations were determined. It was also possible to show where improvements in the design of tools were desirable (Agate and Druett, 1947).

In the latter months of the war an extensive outbreak of cases of Raynaud's phenomenon of occupational origin was discovered in an engineering works where a portable rotary grinding tool was in use. The first cases were reported by Telford and others in 1945. In 1949, Agate, having already surveyed the original outbreak in 1945, traced the later progress of these vascular disturbances by means of follow-up studies. It was shown that at least 77 per cent. of those who had used the particular tool became affected sooner or later, that some of the men were disabled, and that usually the disturbances were progressive and were not relieved by abandoning the work which had caused them.

### OTHER INVESTIGATIONS IN RELATION TO INDUSTRIAL HEALTH

In 1944 Fitzsimons reported gynaecomastia in over half of a group of thirty-two men who were manufacturing stilboesterol. A successful series of counter-measures was evolved. These included enclosing of apparatus, the provision of protective clothing, respirators and washing facilities, selection of staff and limitation of hours of work.

A controlled series of trials as to the value of short wave therapy for the treatment of the common cold was arranged by the Medical Research Council early in the war at the request of the Ministry of Labour and National Service. The results (unpublished) indicated that the symptomatic relief produced by such treatment was insufficient to be of any practical value. Later, a special committee was appointed by the Council

to organise a large-scale field trial in industrial workers and others of the antibiotic 'patulin' in the treatment of the common cold (Medical Research Council, 1944). The results failed to confirm the hopes for this treatment which had been raised in earlier tests on a smaller scale.

Among the aspects of industrial health research which have received increasing study in recent years is that dealing with the rehabilitation of workers suffering from occupational or other disabilities, and their subsequent placement in occupations compatible with their powers. An investigation on these lines was carried out at the London Hospital during the war, special attention being directed to patients with heart disease; it was found possible, by careful job selection, to retain a certain proportion of these patients in industry under conditions in which they could work as satisfactorily as normal individuals.

Such research studies in the rehabilitation of persons with particular forms of disablement have, of course, been accompanied by the development and application at hospitals and other centres of improved rehabilitation methods for the victims of wounds, burns, fractures, spinal injuries and many other clinical conditions. Though the importance of such work from the medical and social points of view can hardly be exaggerated, and great advances were made in it during the war, it belongs to the field of practical therapeutics rather than to that of medical research in the sense covered by the present volume. A number of its aspects are dealt with in other volumes of the Official Medical History.

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# CHAPTER 9

# BIOCHEMICAL RESEARCH

NUMEROUS researches of a biochemical nature have been discussed, albeit briefly, in the previous chapters, and references to the relevant publications have been given. The contents of this chapter fall into three separate groups: (1) a review of certain technical developments of analytical and other laboratory methods, which found useful application under war conditions but have been mentioned only incidentally, if at all, in the accounts already given of diseases in which they are used; (2) a note on early work, particularly in the United Kingdom, on certain medical applications of the researches in nuclear physics with which such rapid progress was made for military purposes during the war; (3) a condensed description of the researches on the chemistry of penicillin which, begun by Chain and Abraham in the School of Pathology at Oxford University early in the war, subsequently formed the subject of a unique Anglo-American co-operative effort.

It should be emphasised again here, as in the Preface, that many very important biochemical studies made by British research workers during the war are omitted from mention in the volume, in that they were of fundamental and long-term interest rather than being immediately related to the war effort. It is probable, moreover, that a considerable number of strictly *ad hoc* investigations has been inadvertently omitted; in such cases apologies are due to the research workers concerned; the task of including all the studies noticed has been formidable, and any attempt to make the volume fully comprehensive would have precluded its publication within a reasonable time.

## Technical Developments: Apparatus and Methods

### PORTABLE COLORIMETERS

The Lovibond comparator sets were supplied to many British hospitals and base units, and they proved of great practical value. The biochemical methods of analysis to which this comparator and the appropriate glass standards lend themselves are simple and numerous, and the apparatus is ideal for field use. Procedures for all the commonly determined constituents of blood and urine were developed by various workers in Great Britain, in collaboration with the late Mr. G. S. Fawcett, Managing Director of Lovibond Tintometer, Ltd.

A portable grey wedge photometer—now known as the M.R.C. photometer—was developed by King and Delory (1944) and King (1947), by the substitution of an annular grey wedge for the coloured

discs used in the Lovibond comparator. Two beams of light pass respectively through a given coloured solution and a segment of the grey wedge; they are collected through a prismatic eyepiece and viewed through a monochromatic light filter; in use the light absorbed by the coloured solution is balanced by rotating the wedge until equal brightness is obtained on both halves of the field. By reading first the standard solution appropriate to any colorimetric method, and then the test solution, it is possible by a simple calculation to determine the concentration of the substance in the test solution. The instrument has a wide range of practical applications, but was devised primarily for haemoglobinometry in the course of an extensive series of studies of the subject, initiated by the Sub-Committee on Analytical Methods of the Traumatic Shock Committee of the Medical Research Council (King, Gilchrist and Delory, 1944; King *et al.*, 1947; Macfarlane *et al.*, 1948; King *et al.*, 1948 *ter*; and Donaldson *et al.*, 1951). The need for improved methods of haemoglobinometry became clear during the large-scale haemoglobin survey among civilians in Great Britain described in Chapter 5. The new photometer was successfully used in the work on anaemia in Indian recruits noticed later in that chapter.

Photo-electric colorimeters (or absorptiometers) were used in considerable numbers by laboratories operating with the American and Canadian Forces, but by only a few of those attached to the British Army.

The determination of mepacrine, the antimalarial drug most widely used by the Allied Forces during the war, requires the use of a fluorimeter. The American fluorimeter, made by Coleman, was supplied to some of the large laboratories and research units operating with the British Forces, as also were a few Hilger fluorimeters. These instruments, while admirably suited to the estimation of mepacrine in the blood plasma, were too costly and difficult to obtain to have any wide application under war conditions. Visual fluorimeters of less elaborate pattern were, however, fairly extensively used for the routine checking of mepacrine concentrations in the blood of soldiers in Italy, Africa, the Middle East and Far East. Simple modifications of the methods of analysis described by Brodie and Udenfriend and by Masen were devised for field use by King and Gilchrist (1945) and by Yudkin (1945).

### PARTITION CHROMATOGRAPHY

The technique of partition chromatography was developed by Martin and Synge at the Wool Industries Research Association laboratories at Leeds, as a means for the separation and estimation of certain amino-acids (Martin and Synge, 1941). As in ordinary or absorption chromatography, the separation is achieved by allowing a solution of the mixture to flow down a tube packed with a granulated or powdered solid

material. In partition chromatography this solid must be non-absorbent but must be capable of loosely retaining water. Silica gel has these properties; the solvent can be chloroform or ethyl acetate or another suitable organic solvent only partially miscible with water.

The mixture to be separated, after preliminary acetylation, which increases the acid strength of the amino-acids and makes them more soluble in organic solvents, is dissolved and allowed to soak into the top of the silica gel. The pure, water-saturated organic solvent is then added, so that it gradually washes the amino-acids down the column. As this progresses, separation takes place into a number of bands, the amino-acids which are more soluble in the moving organic solvent travelling down faster, those that favour the water phase contained in the silica gel moving more slowly. These bands are made visible by the previous incorporation of a suitable indicator such as methyl orange in the silica gel. On issuing from the tube, each band is collected separately and estimated by titration.

Later, Gordon, Martin and Synge (1943) and Consden, Gordon and Martin (1944) modified and extended the method so as to deal with amino-acids without preliminary acetylation. For this purpose, the column of silica gel is replaced by a hanging strip of filter paper, down which an organic solvent can be allowed to percolate. The mixture to be separated is placed near the top of the strip and the whole maintained in a water- and solvent-saturated atmosphere. Separations of complex mixtures can be achieved by developing such a chromatogram down one edge of a sheet of filter paper, drying off the solvent and redeveloping at right angles with a different solvent. The final positions attained by the various amino-acids are revealed as a series of coloured spots by drying off, spraying with a solution of ninhydrin, and heating. The scale of the method using paper is extremely small, amounts of 1 mg. being sufficient for several analyses. A valuable property of this method is that the lower peptides can be separated in the same way as the amino-acids. Where peptides have been separated, the position of the spots can be revealed by the use of insufficient ninhydrin to react with the whole of the substance present. If this is done, the material can then be washed off the paper and identified by further investigations.

Partition chromatography, using both silica gel and filter paper, has been employed for the separation of the penicillins (see section on the Chemistry of Penicillin below). The method has also had wide applications, both during and since the war, for the separation of numerous other biological and pharmacological substances, and as a means of isolating constituents for their determination. The work of Hammick and Firth (1944) on mepacrine and of Morris (1944) on the dye Evans Blue, used to measure blood volume, deserves particular mention in this History.

## Medical Applications of Nuclear Physics

The use of radio-active and stable isotopes in medical research is a development of comparatively recent date. The discovery of deuterium by Urey in 1932, and the devising of methods for its large-scale concentration, paved the way for Schoenheimer and Rittenberg and their colleagues to utilise this heavy hydrogen, a few years later, for their classical investigations on fat and lipoid metabolism. Since then, physicists have made available a large number of natural or stable isotopes of C, N, O, S, etc., and radio-active isotopes of practically every element.

Research in the field of isotopic tracers received a great stimulus during the Second World War, mainly as the result of the preparation of radio-active and stable isotopes in connexion with work on the atomic bomb. With the help of the atomic pile, for example, certain radio-elements are available for biochemical and medical research in quantities which could not possibly be obtained from the most powerful cyclotron. The war also stimulated the development of methods of identification and determination of these special isotopes, and promoted collaboration between physicists, biochemists and other scientists which has greatly facilitated progress in this type of investigation.

For purposes of biological study, a label or tracer, in the form of a stable or unstable (i.e. radio-active) isotope, is attached to the molecule under investigation. Each chemical element is now known to exist in the form of two or more isotopes, the various isotopes of any one element having the same electrical charge on the atomic nucleus, but having different masses. Carbon, for example, can exist as isotopes of masses 10, 11, 12, 13 and 14, i.e. as $^{10}C$, $^{11}C$, $^{12}C$ (the most abundant isotope), $^{13}C$ and $^{14}C$. Of these isotopes, $^{10}C$, $^{11}C$ and $^{14}C$ are radio-active. All the isotopes of carbon behave in the same way in chemical and biological reactions, and the animal body does not, for example, differentiate between a compound containing $^{12}C$ and the same compound containing $^{13}C$.

The ordinary biochemical methods of studying metabolism, although they have yielded an immense amount of very valuable information, have many limitations; often they involve the administration of large excesses of the substance under investigation, or they involve experiments with isolated organs, minced tissue or tissue slices. With the isotopic tracer technique, conditions of a truly physiological nature can be maintained, if care is taken to avoid the use of amounts of radio-isotopes which will cause damage to the tissues by their radiations. The isotopic tracer method thus permits the administration of a compound to a normal animal in normal amounts. Furthermore, it is possible in some cases, using a Geiger-Müller counter, to make a continuous study of the deposition or accumulation of the radio-active 'label' in a certain organ or tissue of the living animal.

The label to be used should be determinable in small amounts, and should cause no change in the chemical and physiological properties of the compounds concerned. Both radio-active and stable isotopes fulfil these requirements, and in the case of many elements (e.g. iron) more than one isotope is available for biological work. It is essential that the label should not be too readily detachable from the molecule by ionisation or by simple chemical exchange.

The isotope tracer method has certain limitations, but these are comparatively few. Some radio-isotopes, for instance, have a half-life period (that period during which half the radio-activity is lost) which is too short for most biological experiments; thus one isotope of fluorine, $^{20}F$, loses half its activity in 12 sec., 75 per cent. in 24 sec. and about 97 per cent. in one minute. In the case of the stable isotopes, those with a fairly high natural abundance (e.g. $^{25}Mg$, which occurs to the extent of 11·5 per cent. in ordinary magnesium) are not usually suitable for biological purposes. It must also be remembered that the use of isotopic tracers merely allows one to obtain information about the fate of the label, or that part of the molecule to which the label is firmly attached.

## PREPARATION AND DETERMINATION OF THE ISOTOPES

(*a*) *Radio-active Isotopes.* These are prepared by the bombardment of suitable elements, or compounds which contain them, with neutrons or deuterons. In the early days, radium-beryllium was used as the source of neutrons. Then came the cyclotron as a powerful producer of neutrons and deuterons. The building of atomic piles, with their abundant supply of neutrons, has, however, completely altered the picture, for in some cases these piles can readily produce radio-isotope preparations more than 1,000 times as active as those produced by a large cyclotron. There is often a choice of several reactions for the preparation of a particular radio-isotope. Thus radio-phosphorus ($^{32}P$), an isotope which has already been used very extensively for biological and medical purposes, has been made by the following methods: neutron bombardment of P (as inorganic phosphate) or of S (as roll sulphur or carbon disulphide) or of Cl (as $CCl_4$, NaCl, etc.) or by deuteron bombardment of S or P. The radio-phosphorus has then to be separated from other radio-active and non-radio-active elements present in the product, but this separation usually presents no great difficulty. The determination of the radio-isotope is made by means of a Geiger-Müller counter, or by a sensitive electroscope, and the activity of tissue extracts can be compared directly with that of standard samples of the starting material used in the investigation. Photographic methods can also be used to detect the radio-isotope in various parts of the treated animal or plant; this auto-radiographic method is the simplest technique for the detection of radio-isotopes, and it is of

special value in showing in which minute structures the labelled element or molecule is deposited.

(*b*) *Stable Isotopes.* These are separated from the more abundant isotopes by elaborate methods such as thermal diffusion and chemical exchange, and in the case of deuterium (heavy hydrogen) by repeated electrolysis. Determination of these isotopes usually requires the costly apparatus known as the mass spectrograph, though deuterium determinations can also be made by accurate measurements of the density or refractive index of the water obtained by combustion of the material to be analysed.

## TRACER ISOTOPES COMMONLY USED IN BIOLOGICAL INVESTIGATIONS

Both types of isotope are widely used in biological research. The determination of the radio-isotope is usually easier, more rapid and more sensitive, but where the isotope has a short half-life there may be considerable decay before the experiment is completed; also, if large amounts of radio-active material are introduced into an animal or plant, there is some danger of tissue changes due to radiation effects. Many of the stable isotopes (e.g. heavy hydrogen or heavy nitrogen) have proved of great value in a variety of biological investigations, and it has been suggested that heavy hydrogen is the most valuable single isotope available to the biochemist. It can also be claimed that the stable isotopes are less foreign to the body than the radio-active; for example, all free and combined glycine in the animal body contains 0·38 per cent. of its N in the form of $^{15}N$ instead of $^{14}N$. 'Isotopic' glycine (i.e. glycine containing much $^{15}N$) need not, therefore, be regarded as a foreign substance.

Usually the choice is one of convenience, often determined by the availability of the material and the facilities for isotope determinations. The stable isotopes of H, N and O, and the radio-isotopes of Na, P, Ca, Fe and I are commonly found convenient for biological work, with a more general use of both types of isotope in the cases of C and S. In some cases, two or three isotopes of the same element have been used in one biological experiment, and there are probably many instances where 'mixed' tracers will yield information not obtainable by the more orthodox methods of biochemistry.

## EXAMPLES OF THE USES OF ISOTOPES IN BIOCHEMISTRY AND MEDICINE

The tracer experiments for which isotopes have been used have included studies on metabolism, nutrition, digestion, absorption, excretion, respiration, immunology, and indeed practically every type of biochemical problem where a labelled or tagged molecule may be helpful. One of the most remarkable general results of these

biochemical studies has been the discovery that practically all the constituents of the animal or plant are in a state of dynamic equilibrium. The proteins of plasma, and those of the various tissues of the body, are constantly being broken down and replaced by fresh protein molecules. Even the most permanent structures like bone (and to a lesser extent teeth) undergo a similar dynamic change, probably in this case mainly or wholly in those areas of the tissue in closest contact with the body fluids.

*Fat Metabolism.* In America Schoenheimer, Rittenberg and their colleagues, using fats and fatty acids containing deuterium, obtained conclusive evidence in support of the view that the animal can desaturate fatty acids, i.e. can introduce one or more double bonds into the fatty acid molecule. These authors have also obtained valuable information regarding the synthesis of cholesterol in the body.

*Creatine Formation.* One of the outstanding feats of metabolic tracer work has been the proof that glycine, arginine and methionine serve as sources of the various parts of the molecule of creatine for the synthesis of this substance in the body.

*Bones and Teeth.* Using $^{32}P$, de Hevesy, in Scandinavia, and many other investigators have shown that there is a constant exchange of phosphate between bone and the body fluids, and that a phosphate radical in the body can be utilised, in a fairly short space of time, for many different branches of metabolism.

*Haemoglobin and the Red Blood Cells.* Much valuable information about the absorption and utilisation of iron by man and other animals has been obtained in America by Whipple and others, with the aid of radio-isotopes of Fe. During the war, similar isotopic work, often involving the use of both $^{55}Fe$ and $^{59}Fe$, was carried out in connexion with blood transfusion and the preservation of whole blood for transfusion purposes. As a result of this work with tagged red cells, it was possible for the Committee on Medical Research in the U.S.A. to establish standards for blood storage. Subsequently more information as to the formation of haemoglobin and the life span of the red blood cell was obtained in experiments involving the administration of $^{15}N$ -containing glycine.

*The Action of Vesicants.* The use of mustard gas containing radio-S ($^{35}S$) gave information on the rate of penetration through the skin and on the fate of this vesicant in the animal body (Kistiakowsky, Henriques, Moritz and others in the U.S.A.; Young in Canada; and Wormall and his colleagues in Great Britain (see Chapter 10)).

*Other Applications.* Among these may be mentioned the use of $^{14}C$ and $^{11}C$ in studies on respiration, radio-iodine for investigations on thyrotoxine and the thyroid gland, $^{32}P$ for the study of phosphatide metabolism, and $^{15}N$ for the study of protein metabolism.

The use for diagnostic or therapeutic purposes of radio-isotopes with special affinities for particular tissues, though of great practical importance in medicine, is outside the scope of this volume.

## The Chemistry of Penicillin

When the investigation of penicillin was begun at Oxford, as described in Chapter 7, little was known about the chemical nature of the penicillin molecule beyond the fact that it was an acid of low molecular weight, which appeared to pass to a large extent into ethereal solution from the acidified culture fluid; Clutterbuck, Lovell and Raistrick, in their work published in 1932, had found that the ethereal extract lost most of its antibacterial activity on evaporation. The Oxford workers showed that the biological activity of penicillin could be retained without appreciable loss when the extraction into ether or other organic solvents from the acidified culture medium was carried out at temperatures of from 0° to +7° C., and the extracted acids were subsequently transferred from the organic solvent into water by adding the correct amount of alkali to bring the *p*H to neutrality. The neutral aqueous solution could be evaporated to dryness from the frozen state *in vacuo* without loss of activity, and in this way a dry preparation containing an alkali salt of penicillin was obtained, which kept its considerable antibacterial activity undiminished for at least several days. With such preparations it was shown that mice could be protected from fatal infections with streptococci, staphylococci and *Cl. septicum*, and later the value of purer preparations for the treatment of severe systemic and local infections with penicillin-sensitive bacteria in man was demonstrated (Abraham, Gardner, Chain, Heatley, Fletcher, Jennings and Florey, 1941).

### RESULTS OF EARLY CHEMICAL WORK AT OXFORD

Penicillin was found to lose its biological activity rapidly in aqueous solution at room temperature at both acid and alkaline *p*H's, but it was stable between *p*H 5 and *p*H 7. At temperatures between 0° and +7° C. it was found to be sufficiently stable in acid solution to permit its extraction into organic solvents without appreciable loss. Once in the organic solvent, penicillin was stable for indefinite periods. In the course of attempts to prepare different salts it was found that penicillin was rapidly inactivated by many metallic ions, in particular those of zinc, cadmium, copper and lead, and also by an excess of ammonia and primary organic bases. When the solubility of penicillin in organic solvents was studied, it was observed that the alkali salts rapidly lost their biological activity in primary alcohols. Penicillin was shown to be inactivated by ketonic agents such as hydrazine and hydroxylamine. It was found to be sensitive to oxidising agents, but stable to reducing agents acting at neutral *p*H, such as catalytically activated hydrogen

and aluminium amalgam. In view of the sensitivity of penicillin to many reagents usually employed for purification purposes, the methods that could be used for its purification were limited to partition between water and different solvents, and to various forms of chromatography. By combining such methods with a reduction process involving the use of aluminium amalgam, a preparation of the barium salts of penicillin of about 50 per cent. purity was obtained. Electrometric titrations showed that penicillin possessed no basic group, but after inactivation with acid and with alkali, new basic groups with *p*H values of 7·6 and 5 respectively and two new acid groups appeared. Thus it was shown that penicillin was transformed by these processes into two different products of zwitterionic nature, and that a carboxyl group present in bound form in the penicillin molecule was set free. It was also shown that penicillin was decarboxylated when heated in acid solution at 80–100° C. These observations were recorded in a paper by Abraham and Chain (1942). The same authors had previously demonstrated the existence in some penicillin-resistant bacteria of an enzyme, capable of destroying penicillin, which was termed penicillinase (Abraham and Chain, 1940).

Analysis of the purified preparation of penicillin showed that it contained nitrogen (Abraham, Baker, Chain, Florey, Holiday and Robinson, 1942). It was stated by the micro-analysts to be sulphur-free, but this proved to be an error, and caused considerable delay in the correct interpretation of the results of subsequent chemical degradations.

By this time (1942) Dr. Wilson Baker and Sir Robert Robinson, of the Dyson Perrins Laboratory, Oxford, had joined Drs. Chain and Abraham in the chemical investigations on penicillin. All the work on degradation products was carried out by this group of chemists, who were joined in the synthetic studies by Dr. J. W. Cornforth and later by many other members of the staff of the Dyson Perrins Laboratory. Dr. E. R. Holiday, of the London Hospital, working in the Department of Biochemistry, Oxford, collaborated by measuring ultra-violet absorption spectra.

Shortage of material was an ever-present and serious handicap to the degradation work at Oxford, which was carried out mainly with penicillin preparations made in the small production plant at the Sir William Dunn School of Pathology. In these circumstances the work was greatly facilitated by the collaboration of Drs. D. Crowfoot and B. Low of the Department of Crystallography, Oxford, who carried out X-ray crystallographic studies on breakdown products and were thus able to provide valuable physico-chemical data, making possible the identification of compounds available only in minute amounts.

Meanwhile, other groups of chemists in England had become interested in the chemistry of penicillin. The Department of Organic Chemistry at the Imperial College of Science, London, the Glaxo

Laboratories, the laboratories of Imperial Chemical (Pharmaceuticals) Ltd., and those of the Wellcome Foundation started investigations, and during the later stages the following groups also took part: the Department of Chemistry at Manchester University; the Departments of Chemistry and Colloidal Science at Cambridge; the National Institute for Medical Research; the Department of Physical Chemistry at Oxford; the British Drug Houses, Ltd.; Boots Pure Drug Company, Ltd.; and Imperial Chemical Industries, Ltd. (Alkali Division).

In view of the importance of penicillin for war medicine and the difficulties that were encountered at that time in its production on a large scale by the fermentation process, it was recognised that a workable synthesis would be a major contribution to the war effort of the side possessing it. To prevent the enemy from obtaining valuable information, a security ban was imposed in 1943 by the Governments of Great Britain and the U.S.A. on all matter relating to the chemistry of penicillin. This ban remained in force till the end of 1945. The British chemists working on penicillin formed a committee consisting of representatives of the different groups, in order to exchange information. Dated progress reports, known as the 'PEN' series, were sent to the secretary of the committee, and it was agreed that these should be regarded as equivalent to publications which in the normal course of events would have been sent to scientific journals. The contents of these and other unpublished reports were subsequently incorporated in the monograph *The Chemistry of Penicillin*, published in 1949 under joint British and American authority; accordingly, though these documents are mentioned in the text of the present account, they are not included in the list of publications at the end of the chapter.

## CRYSTALLINE DEGRADATION PRODUCTS

The first crystalline degradation product of penicillin was an amino-acid termed penicillamine (Abraham, Chain, Baker and Robinson, 1943). Though the penicillin then available was not more than 50 per cent. pure, there were several indications that penicillamine was a genuine degradation product and did not arise from an accompanying impurity. It was therefore decided to press on with the elucidation of its structure, and not to wait until the final purification of penicillin had been achieved.

Soon after the isolation of penicillamine, workers at the Wellcome Chemical Laboratories isolated another crystalline degradation product of penicillin, termed penillic acid (Duffin and Smith, 1943). This substance was formed on inactivation of penicillin at *p*H 2. Shortly afterwards the Oxford workers (PEN 79, May 1943) reported the isolation of a substance termed penicillinic acid from acid-inactivated

penicillin, which was very similar to penillic acid, but not identical with it crystallographically. (This was later shown to be a crystalline modification of penillic acid which is formed when $\Delta^2$-pentenylpenillic acid crystallises together with a small amount of benzylpenillic acid). The finding on analysis that penillic acid and penicillinic acid contained 14 carbon atoms made it almost certain that penicillin did so, since no fission compound with one or two carbon atoms could be detected on its inactivation with acid. On hydrolysis with dilute acid at 100° C., penicillinic acid behaved like penicillin itself, giving penicillamine and one molecule of carbon dioxide; on treatment with mercuric chloride, it also yielded carbon dioxide and was converted into a base termed penillamine, which was also obtained from penillic acid by the same method (Duffin and Smith, PEN 86, July 1943).

The structure of penicillamine was elucidated as follows. On treatment with bromine water it gave a crystalline oxidation product termed penicillaminic acid (Abraham, Baker, Chain and Robinson, PEN 79, May 1943). Analysis of this product gave very high oxygen figures which could not be explained by the presence of water of crystallisation. This led to the suspicion that the compound contained sulphur, and the presence of this element in penicillin and in all the degradation products was soon established. The recognition of sulphur as a constituent of the penicillin molecule allowed the correct formulae to be put forward for penicillamine ($C_5H_{11}O_2NS$), penicillaminic acid ($C_5H_{11}O_5NS$), penillic acid ($C_{14}H_{20}O_4N_2S$), and penillamine ($C_{13}H_{20}O_2N_2S$) (Abraham, Baker, Chain and Robinson, PEN 88, July 1943; Duffin and Smith, PEN 90, August 1943). It also became clear at once that penicillamine was a thiolamino-acid; penicillaminic acid was the corresponding sulphonic acid; and the base penillamine, but not penillic acid or penicillin, contained a free thiol group. Penicillamine was shown to be an $\alpha$-amino-acid which formed readily an isopropylidene compound with acetone, showing that the $\alpha$-amino and thiol groups were in juxtaposition. The fact that penicillamine gave only a fraction of a molecule of acetic acid on oxidation with chromic acid suggested that it contained a gem-dimethyl group and had the structure of $\alpha$-amino-$\beta$-thiolisovaleric acid, an amino-acid hitherto not encountered in nature (Abraham, Baker, Chain and Robinson, PEN 97, September 1943). This was confirmed by synthesis (Abraham, Baker, Chain, Cornforth, Cornforth and Robinson, PEN 100, October 1943), and it was shown that penicillamine had the D-configuration.

### PURIFICATION OF PENICILLIN

Meanwhile, work on the purification of penicillin was continued. The Imperial College team achieved considerable purification of

penicillin solutions in organic solvents by partition chromatography on silica gel impregnated with barium carbonate (Catch, Cook and Heilbron, 1942), while the Oxford and I.C.I. workers used partition chromatography on silica gel containing phosphate buffer, a modification of the method introduced by Martin and Synge (1941) for the separation of amino-acids. In July 1943, preparations of the barium salts of penicillin were obtained at Oxford that gave penillic acid in 75 per cent. yield, indicating that a high degree of purity had been achieved (PEN 87, July 1943).

At the same time, the Squibb Institute for Medical Research and Merck and Co., Inc., in the U.S.A., had made great progress in the purification of penicillin, and in August 1943 the Medical Research Council learnt by telegram that Wintersteiner and McPhillamy, of the Squibb Institute, had succeeded in obtaining the sodium salt of penicillin in the crystalline state, and that it had the composition $C_{16}H_{17}O_4N_2SNa$. On receipt of this information, the purest barium salt of penicillin obtained at Oxford was converted into the sodium salt and was found to crystallise spontaneously (Abraham, Baker, Chain and Robinson, PEN 94, September 1943; Crowfoot and Low, PEN 96, September 1943). The analytical figures of the purest preparations of the barium salt of penicillin obtained at Oxford gave the empirical formula $C_{14}H_{19}O_4N_2SBa_{(\frac{1}{2})}$, which showed that the British penicillin differed in composition from the American. Differences in the composition of the British and American penicillins had been suspected for some time, as it became known in England through private information that the American workers had isolated phenylacetic acid from the hydrolysis products of their penicillin, an easily recognisable product that had not been encountered by the British workers during their degradation studies. The analytical figures for penicillin made it clear that penillic acid was an isomerisation product of penicillin. In England the British and American penicillins were designated with the Roman figures I and II respectively, while in the U.S.A. they were referred to as penicillins F and G.

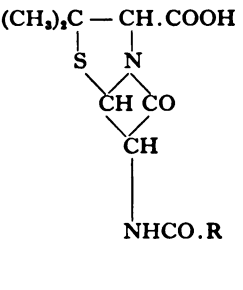
With the isolation and identification of penicillamine ($C_5H_{11}O_2NS$), five of the 14 carbon atoms of penicillin-I had been accounted for. A sixth carbon atom was accounted for by the molecule of carbon dioxide that was liberated by acid hydrolysis of penicillin or by treatment of its isomerisation product penillic acid with mercuric chloride. The remaining eight carbon atoms were found in an aldehyde, $C_8H_{13}O_2N$, which was isolated in small yield from acid hydrolysates of penicillin (after removal of penicillamine with mercuric chloride) in the form of its 2:4-dinitrophenylhydrazone (Abraham, Chain, Baker and Robinson, PEN 91, August 1943). It was obtained in better yield from alkali-inactivated penicillin after treatment with mercuric chloride (Abraham, Baker, Chain and Robinson, PEN 97, September 1943). The aldehyde

was later designated as penilloaldehyde. Working with catalytically reduced penicillin-I, the Imperial College team isolated dihydropenillo-I aldehyde ($C_8H_{15}O_2N$), which on heating with 2:4-dinitrophenylhydrazine yielded glyoxal-*bis*-2:4-dinitrophenylhydrazone (a product previously found by Oxford workers on heating penicillin-I with 2:4-dinitrophenylhydrazine (Abraham, Chain, Baker and Robinson, 1943), and they ascribed the structure $C_5H_{11}CO.NH.CH_2.CHO$ to dihydropenillo-I aldehyde (Bentley, Catch, Cook, Heilbron, Hall and Elvidge, PEN 102, October 1943). The Oxford workers put forward the structure $C_5H_9CO.NH.CH_2.CHO$ for penillo-I aldehyde, because (i) the acid $C_8H_{13}O_3N$, obtained from penillo-I aldehyde by oxidation with silver oxide, contained its nitrogen in a peptide linkage, giving an α-amino-acid on hydrolysis with acid or alkali, and (ii) if phenylacetic acid was a constituent of the American penicillin, it could only be derived from a penilloaldehyde of the structure $C_6H_5CH_2CO.NH.CH_2CHO$ (Abraham, Baker, Chain and Robinson, PEN 103, October 1943). The isolation of glycine from the hydrolysis products of the acid $C_8H_{13}O_3N$ confirmed the structure $C_5H_9CO.NH.CH_2.CHO$ for penillo-I aldehyde (Abraham, Baker, Chain and Robinson, PEN 109, November 1943). The workers at Imperial College (PEN 105, October 1943) isolated *n*-caproic acid from dihydropenillo-I aldehyde and thus proved that it had the structure of *n*-caproylamino-acetaldehyde. The double bond in the hexenoic acid moiety of penillo-I aldehyde was shown to be in the βγ-position by oxidation with permanganate (yielding propional) and thus penillo-I aldehyde was proved to be βγ-hexenoylaminoacetaldehyde (PEN 109). Both caproylaminoacetaldehyde and βγ-hexenoylaminoacetaldehyde were synthesised (Abraham, Baker, Chain and Robinson, PEN 109, November 1943) and their identity with the natural penilloaldehydes confirmed.

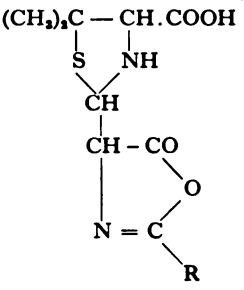
Thus it had been established that the penicillin molecule was built up of three components: the amino-acid penicillamine and a labile carbon dioxide group, which were common to the different penicillins, and an acylated amino-acetaldehyde, the acyl group of which varied in the different penicillins. The penicillins could be hydrolysed into these components, with the participation of two molecules of water, according to the equations:

penicillin-I $C_{14}H_{20}O_4N_2S + 2H_2O = C_5H_{11}O_2NS + C_8H_{13}O_3N + CO_2$
penicillin-II $C_{16}H_{18}O_4N_2S + 2H_2O = C_5H_{11}O_2NS + C_{10}H_{11}O_2N + CO_2$

Many formulae for the penicillin molecule can be devised by linking together the three components with the elimination of two molecules of water. On the basis of the evidence then available the formulae (**I**) and (**II**) were suggested by the Oxford workers (Abraham, Baker, Chain and Robinson, PEN 103, October 1943):



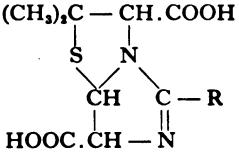
I



II

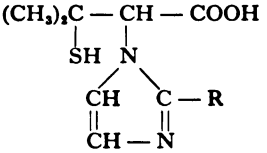
Formula (**I**), which was later proved to be the correct structure, was more favoured by the majority of the workers (despite the fact that it contained the unusual 4-membered ring) because it alone could explain satisfactorily the absence of a basic group in the penicillin molecule.

Simultaneously, the correct structure for penillic acid (**III**)



III

was put forward (PEN 103, October 1943). On the basis of its physico-chemical properties and its behaviour on degradation, penillamine, the decarboxylation product of penillic acid, could have only one structure, that of the imidazole derivative (**IV**):



IV

This formula was suggested by the workers at Imperial College (PEN 106, October 1943) and was implied in the formula for penillic acid suggested by the Oxford workers.

Meanwhile, an increasing volume of work on the constitution of the penicillins was carried out in the U.S.A., independently of the British researches. The British workers, however, had little knowledge of the American investigations in the early stages.

### COLLABORATIVE ANGLO-AMERICAN EFFORTS

At the beginning of 1944, when the British work on degradation products, described above, was completed, the Medical Research Council took over the co-ordination of the chemical research on

penicillin in Great Britain, and formed a Committee for Penicillin Synthesis (Appendix I). Negotiations between the Council and the Office of Scientific Research and Development in the U.S.A. were conducted with the aim of establishing closer contact between the British and American workers. Agreement on a regular exchange of progress reports by workers in the two countries was reached early in 1944. This exchange of information continued until the end of 1945, and the magnitude of the collaborative research effort can be gauged from the fact that nearly 700 reports were received by the co-ordinating Government organisations.

The following American academic, governmental and industrial laboratories participated in this work: U.S. Department of Agriculture, Northern Regional Research Laboratory; Cornell University Medical College, Department of Biochemistry and Russell Sage Institute; Federal Security Agency, Food and Drugs Administration; Harvard University, Department of Chemistry; University of Illinois, Department of Chemistry; University of Michigan, Departments of Chemistry and Physics; National Bureau of Standards; Rockefeller Institute for Medical Research at Princeton; the Abbott Laboratories; Cutter Laboratories, Inc.; Heyden Chemical Corporation; Eli Lilly and Co.; Merck and Co., Inc.; Parke, Davis and Co.; Chas. Pfizer and Co., Inc.; Shell Development Company; Squibb Institute for Medical Research; the Upjohn Company and Winthrop Chemical Co., Inc.

American progress reports were submitted monthly to the Office of Scientific Research and Development. Each was dated and given a letter indicating the laboratory where the work was carried out, followed by a number—for example Merck M-1. The British reports sent to the Committee for Penicillin Synthesis of the Medical Research Council were termed CPS reports and each was given a CPS number.

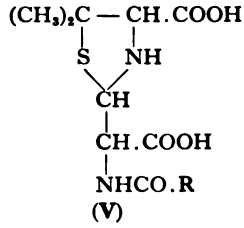
The work summarised in the reports related to: (i) degradation studies on penicillin, (ii) the synthesis of model compounds for the different structures suggested for the penicillin molecule, (iii) the synthesis of degradation products of penicillin, and (iv) the synthesis of intermediates for projected syntheses of penicillin.

The first American reports reached the British teams in April 1944, and it became apparent at once that the degradation of the American penicillin had given results analogous to the British work, as expected. The American penicillin had yielded carbon dioxide, penicillamine, and a penilloaldehyde which differed from the British penilloaldehyde in that it contained the phenylacetyl group instead of the hexenoyl group (Merck and Co., Report of October 1943). Thus, it was clear that the two penicillins had a common nucleus, but differed from each other by the nature of a side chain. Later, other penicillins possessing side chains different from those of penicillins I and II became known. It was finally agreed to designate the different penicillins by a prefix

indicating the nature of the side chain. Thus, penicillin-I was designated $\Delta^2$-pentenylpenicillin, penicillin-II as benzylpenicillin, and so on. The degradation products were designated in a similar manner, e.g. benzylpenillic acid, $\Delta^2$-pentenylpenillamine. In the subsequent account this nomenclature will be followed.

An important contribution to the structural studies, made by the Merck group, was the proof that the labile carboxyl group in the penicillin molecule giving rise to carbon dioxide on heating in acid solution was the carboxyl group present in bound form. This was shown by degradation with mercuric chloride of the inactivation product obtained after treatment of benzylpenicillin with benzylamine (which was first isolated in the crystalline state by workers at the Northern Regional Research Laboratory) and also by mercuric chloride degradation of the methanol inactivation product.

Both products gave the insoluble mercuric complex of penicillamine, and from the supernatant solution derivatives of a β-aldehydo-acid were isolated, which was termed penaldic acid. The benzylamine inactivation product gave the benzylamide of penaldic acid, which on catalytic reduction could be converted into the cyclohexylamide of cyclohexylacetylserine; the methanol inactivation product gave the methyl ester of penaldic acid, which could be converted by catalytic reduction to cyclohexylacetylalanine (Merck and Co., M-1 and 2, November 1943). These findings settled the structure of the products obtained on the inactivation of benzylpenicillin with methanol, benzylamine and alkali. They were derivatives of a thiazolidine which was termed penicilloic acid and had the structure shown in formula (**V**):



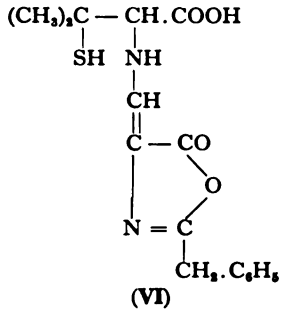
(**V**)

Benzylpenicilloic acid was isolated in the form of its crystalline sodium salt from alkali-inactivated penicillin. It and many derivatives (mono- and di-esters, amides and their *N*-acyl derivatives) were synthesised. The stereo-chemistry of the penicilloic acids was studied in detail by the Merck group, and derivatives of all four theoretically possible isomers of penicilloic acid, deriving from D-penicillamine, were isolated.

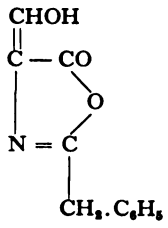
The workers of the Merck group had advanced as the most likely structure for the penicillin molecule the thiazolidine-oxazolone structure (**II**); other possibilities, among them the β-lactam structure (**I**), were considered less likely. The thiazolidine-oxazolone structure was for some time most favoured by the majority of workers, but as the

investigations progressed, evidence accumulated which was difficult to reconcile with this structure, but was compatible with the β-lactam structure. Many thiazolidines with a free imino group such as that present in the thiazolidine-oxazolone structure, and with an acylated imino group, as in the β-lactam structure, were synthesised. Their study revealed that thiazolidines with free imino groups had properties differing markedly from those of penicillin, whereas the *N*-acylated thiazolidines showed a similar behaviour. Thus, the former had basic groups, shown by salt formation and electrometric titrations, were oxidised by iodine, poisoned irreversibly platinum and palladium hydrogenation catalysts (Eli Lilly workers), and gave sulphonic acids on oxidation with permanganate; the *N*-acylated thiazolidines showed no basic groups, were stable to iodine, did not poison hydrogenation catalysts and gave sulphones on oxidation with permanganate. The penicillins showed no basic group, and did not react with iodine. $\Delta^2$-pentenylpenicillin could be reduced readily to amylpenicillin in the presence of platinum or palladium catalysts, and the methyl ester of benzylpenicillin gave a sulphone (Merck and Co., M-54, January 1945) on oxidation with permanganate. Many oxazolone models were synthesised. Those possessing a structure similar to the oxazolone present in the thiazolidine-oxazolone structure, i.e. saturated in the 2-position, were shown to be much less stable in aqueous solution than the penicillins. Thus, the study of model thiazolidines and oxazolones gave results incompatible with the thiazolidine-oxazolone structure, but in agreement with the β-lactam structure.

On the other hand, studies of the degradation products of penicillin gave ambiguous results. Workers of the Merck group showed that in addition to the intramolecular rearrangements to penillic acid, the penicillin molecule was capable of undergoing two further intramolecular rearrangements. On treatment of the methyl ester of penicillin with mercuric chloride, benzylpenicillin was transformed into the methyl ester of the isomeric penicillenic acid (**VI**). This could be hydrolysed by alkali into penicillamine and 2-benzyl-4-hydroxymethylene-5-oxazolone, which was isolated in the form of its crystalline sodium salt (**VII**) (Merck and Co., M-46, October 1944).

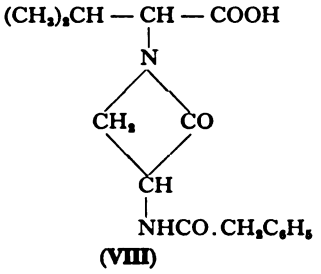


(VI)



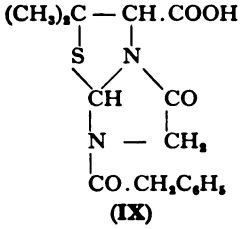
(VII)

The isolation of one component of the thiazolidine-oxazolone structure was naturally a strong argument in favour of this structure. Its significance, however, was offset by the isolation of a degradation product, $C_{16}H_{20}O_4N_2$, obtained from natural sodium penicillin by hydrogenolysis with Raney nickel under mild conditions and termed desthiopenicillin, which was shown to possess the β-lactam structure (**VIII**) (Merck and Co., M-46, October 1944; M-49, November 1944).



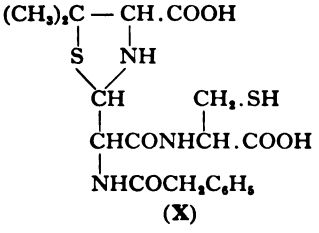

(**VIII**)

Another isomerisation product of benzylpenicillin, termed penillonic acid, was obtained by heating the methyl ester in toluene in the presence of a trace of iodine (Merck and Co., M-36, July 1944; M-39, August 1944). The elucidation of its structure as an imidazolone derivative (**IX**) did not contribute conclusive evidence in favour of either one or the other of the two structures for the penicillin molecule.



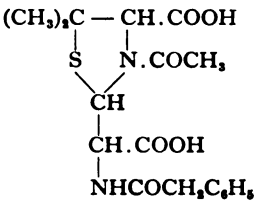

(**IX**)

A number of other reactions of penicillin were discovered. Thus, it was found by the Squibb group (S-5, February 1944) that benzylpenicillin was inactivated by cysteine; the inactivation product was shown to be a peptide of penicilloic acid and cysteine, with the cysteine SH group free (**X**).



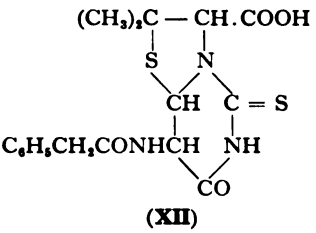

(**X**)

The Squibb group also discovered that free benzylpencillin reacted with acetic acid to give *N*-acetyl benzylpenicilloica cid (**XI**). Both these reactions could be explained on the basis of either the thiazolidine-oxazolone or the β-lactam structure.



**(XI)**

The Cornell group obtained a crystalline product on the reaction of thiocyanic acid with benzylpenicillin. Oxazolones are known to react with thiocyanic acid to give 1-acylthiohydantoins. The reaction product of benzylpenicillin with thiocyanic acid, however, was shown to give a thiodihydrouracil of the structure shown in (**XII**).



**(XII)**

The formation of this compound could be explained better on the basis of the β-lactam structure than the thiazolidine-oxazolone structure, though the possibility of an intramolecular rearrangement leading from the thiazolidine-oxazolone structure to the thiodihydrouracil could not be excluded.

A considerable amount of work on infra-red spectra was carried out in England by H. W. Thompson and R. E. Richards of Oxford and by G. B. B. M. Sutherland of Cambridge; and in the U.S.A. by workers at the University of Michigan, Cornell University Medical College, Russell Sage Institute, the laboratories of Merck and Co., Inc. and the Shell Development Company. The results of these studies could not at first be reconciled with either of the two structures, but when synthetic models more closely related to the β-lactam structure became available (fused thiazolidine-β-lactam, synthesised by the Shell group, γ-lactam homologue of benzylpenicillin, synthesised by the Cornell group), the infra-red studies of these compounds supported on the whole the β-lactam structure.

Final proof for the β-lactam structure was provided by remarkable X-ray crystallographic studies, on crystals of the sodium, potassium

and rubidium salts of benzylpenicillin, carried out by Crowfoot and Low of Oxford University (CPS 508, May 1945) and confirmed by Bunn and Turner Jones (Alkali Division, Imperial Chemical Industries, Ltd., Northwich). By Fourier analyses in three dimensions, the bond distances between all atoms of the benzylpenicillin molecule were measured, and the whole molecule mapped out. The presence of the four-membered β-lactam ring in the penicillin molecule was clearly demonstrated.

### SYNTHETIC WORK

Most of the degradation products of penicillin have been synthesised. Several syntheses for pencillamine, penaldic acid and its derivatives, penillic acid (Merck and Co., M-50, November 1944; Imperial College workers, CPS 199, July 1944), penillamine (Oxford workers, CPS 71, June 1944; Imperial College workers, CPS 67, May 1944), penicilloic acid and its derivatives and penicillenic acid (Merck and Co., M-12a, February 1944) have been developed. In addition to thiazolidine and oxazolone models, various β-lactam models (Merck and Co., Chas. Pfizer and Co., Shell Development Company), and the γ-homologue of penicillin which proved biologically inactive (Cornell group, D-26, February 1945) have been synthesised.

The synthesis of penicillin itself was approached by different routes. Ring closure of penicilloic acid and its derivatives, attempted by numerous methods, gave no results. In attempts to synthesise the thiazolidine-oxazolone structure by condensation of D-pencillamine with an appropriate hydroxymethylene-oxazolone, the Merck group obtained a trace of antibacterial activity using D-pencillamine and 2-methoxymethylene-4-benzyl-5-oxazolone (M-10, January 1944). Independently, the Oxford workers obtained a trace of activity by condensing D-pencillamine with 2-hydroxymethylene-4-styryloxazolone (CPS 35, March 1944). Similar condensations were carried out with other substituted 2-hydroxymethylene-oxazolones. The activity was shown to be destroyed by penicillinase (Oxford workers, CPS 648, November 1945), and it was therefore concluded that substances of the penicillin type had been synthesised.

This view was supported by the finding of the Cornell group (D-27, March 1945) that the synthetic antibacterial material acted against the same bacteria, and quantitatively in the same manner, as natural benzylpenicillin. Further evidence for the identity of the synthetic antibacterial substance with natural benzylpenicillin was obtained by the Cornell group, using the isotope dilution technique (D-36, November 1945). Many unsuccessful attempts to improve the yield of the synthetic penicillin were made.

Though the result of the concerted effort of many chemists to produce an economic method of synthesis of natural penicillins and

structurally related compounds has been disappointing, two methods of producing modified penicillins have been developed, both involving the biological mould fermentation process. Through isolation of a new penillic acid and the study of its chemical composition, the Imperial College workers (CPS 23, February 1944) produced evidence for the existence of a new penicillin, containing the *p*-hydroxybenzyl side-chain. This penicillin proved to be identical with a chloroform-insoluble penicillin observed in the Cutter Laboratories and the Northern Regional Research Laboratory in the U.S.A., and it was isolated in the form of the crystalline sodium salt by workers in the latter centre (C-9, August 1944). It was shown in the same laboratory that iodine and different azo groups could be introduced into the *p*-hydroxybenzyl side-chain of the new penicillin without loss of its antibacterial activity, and a number of 'azopenicillins' have already been prepared in this way.

Stimulation of the yield of penicillin following the addition of phenylacetic acid and its derivatives to the mould culture medium was observed by workers at the Northern Regional Research Laboratory (Report to the Committee on Medical Research, November 20, 1943). Experiments by the Imperial College workers (CPS 291, October 1944) indicated that the phenylacetic acid was actually incorporated by the mould into the penicillin molecule. The Eli Lilly group demonstrated that derivatives of phenylacetic acid with substitute groups in the benzene nucleus, such as *p*-methoxy-phenylacetic acid, *p*-fluoro-phenylacetic acid, etc., were also utilised by the mould for penicillin synthesis and new penicillins were formed in this manner. Several of these semi-artificial penicillins were isolated in the form of their crystalline sodium salts.

Although the penicillins resisted all attempts at a satisfactory synthesis, the partial synthesis of a number of new penicillins from one naturally occurring was an achievement of great importance. While there was no indication that penicillins produced in this way would prove useful in the treatment of infections due to organisms resistant to the natural penicillins, it was obvious that these substances were worthy of systematic study, both because the relationship between activity and any modification in structure is of general theoretical interest, and because varieties of penicillin might well be found whose solubilities and rates of excretion from the body would render them superior to the natural products for clinical use.

The penicillin molecule has been shown to contain a new ring system, previously unknown in nature; the chemical reactivity of this system, its rearrangements to new configurations, and the way in which it can disorganise the biochemical processes of the bacterial cell, raise problems whose solution would represent a notable addition to our knowledge of both theoretical and biological chemistry.

## Publications relating to Chapter 9


### TECHNICAL DEVELOPMENTS: APPARATUS AND METHODS

CONSDEN, R., GORDON, A. H. and MARTIN, A. J. P.—
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# CHAPTER 10

# CHEMICAL DEFENCE RESEARCH

MEDICAL research on chemical warfare problems was carried out under the supervision of the Chemical Board of the Ministry of Supply, with the aid of various sub-committees; these bodies included the Physiological Sub-committee (Chairman, Professor Sir Joseph Barcroft until 1942; Professor C. G. Douglas from 1942), the Medical Sub-committee (Chairman, one of the senior medical staff officers of the Armed Forces), the Biochemical Sub-committee (Chairman, Professor R. A. Peters), the Chemical Factories Medical Sub-committee (under the chairmanship successively of Professor Sir Joseph Barcroft, Professor J. A. Ryle and Professor C. G. Douglas), and the Ophthalmic Panel (Chairman, Professor C. G. Douglas). The Chemical Factories Medical Sub-committee was concerned with the health of the employees at chemical warfare factories and with the treatment of accidental injuries due to chemical warfare agents.

The majority of the experimental work sponsored by the Board was undertaken at the Ministry of Supply Chemical Defence Experimental Station, Porton, where the small peace-time medical staff was augmented by professors and lecturers from universities, by British Service medical officers, and later by medical officers from the U.S. Army and Navy Medical Corps. Much relevant research work was done, also, by teams of investigators at various universities, under contract with the Ministry of Supply. Co-ordination of the research programme with the needs and problems of the Armed Forces and of the civilian population was ensured by the choice of scientists to serve on the sub-committees and by frequent visits of the members of these bodies to the Experimental Station. The Air Raid Precautions Department of the Home Office and the Ministry of Home Security was represented on the sub-committees, and was thus enabled to keep hospitals and civilian medical practitioners informed of the latest methods of treating gas casualties.

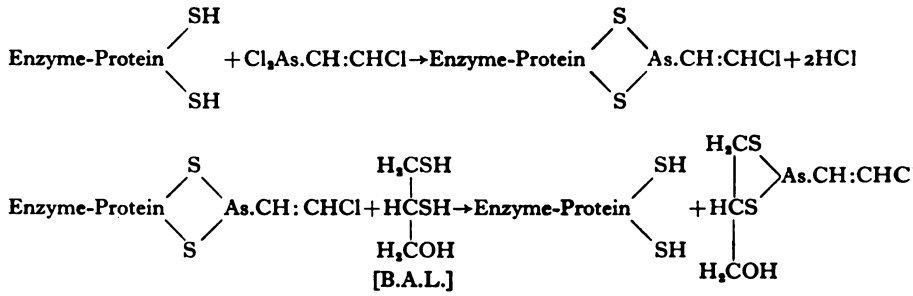
Throughout the war it was envisaged that, in the event of the initiation of chemical warfare by the enemy, the main attack might be with vesicants, such as mustard gas or the chlorinated amines known as the 'nitrogen vesicants', or with arsenical vesicants such as lewisite, or perhaps by some potent agent hitherto unknown; the possibility of attack by lethal agents such as phosgene and cyanogen compounds was also considered. Accordingly, intensive research was organised at the Ministry of Supply Experimental Station and at universities, on the modes of action of mustard gas and similar vesicants, of phosgene and of cyanogen compounds, on the treatment of mustard gas burns and of

phosgene poisoning, and on protective measures such as respirators, anti-gas ointments and protective clothing. Pathological work on the lesions produced by various chemical warfare agents was carried out at the Experimental Station by a team working under the direction of Professor G. R. Cameron.

Groups of scientists at various universities assisted in the research programme. The general idea underlying the work was that chemical warfare agents produce their harmful effects on the tissues by a specific chemical attack on some essential cell constituent: if, therefore, this could be identified and the nature of the reaction determined, it might be possible to devise a treatment to prevent or even reverse the reaction. This was successfully achieved in the case of one class of poisons (the arsenicals) by Professor R. A. Peters and his colleagues at Oxford, as described below.

### THE DEVELOPMENT OF 'B.A.L.'

It had been known for some time, as a result of investigations both in Great Britain and in the U.S.A., that arsenicals combined with thiol (-SH) groups to form thioarsinite linkages, and that some of these linkages were reversible. It was also known that the toxic action of trivalent arsenicals was selective among various enzymes, and that, in particular, some component of the pyruvate oxidase system of enzymes was poisoned by mere traces of arsenite. It had been suggested by Peters before the war that this enzyme system might be susceptible to vesicants. The search for an antidote to lewisite started with the belief that this arsenical poisoned selectively an -SH group in the pyruvate oxidase system; the pyruvate oxidase system was taken as a representative enzyme, a view strengthened by the proof that it contained -SH groups and that arsenical poisoning induced a rise in the pyruvic acid content of the blood. Monothiols had no effect *in vitro* or *in vivo* upon poisoning by lewisite, as the lewisite had a greater affinity for the poisoned tissue component; evidence was obtained by Stocken and Thompson from analysis of arsenical-kerateine compounds that this affinity was due to combination of the arsenic atoms with two neighbouring thiol groups in the protein to form a stable ring compound. This suggested that a dithiol compound might be prepared which would have a still greater affinity for arsenic, removing the 'arsenic' from the enzyme and so reversing the poisoning. The dithiol compound 2:3 dimercaptopropanol ($CH_2SH.CHSH.CH_2OH$) was early synthesised and was found to restore the activity of the pyruvate oxidase system *in vitro* after poisoning by lewisite (Peters, Stocken and Thompson, 1945; Peters, 1948; Thompson, 1948). This antidote, less toxic than other compounds of similar type, was called by the Americans 'B.A.L.' or 'British Anti-Lewisite'. Its mode of action against lewisite is illustrated overleaf. When tested in the treatment of lewisite burns,




A ring compound is formed by the combination of the lewisite with a protein component of the enzyme (pyruvate oxidase system), blocking the action of the enzyme. B.A.L. forms a more stable ring with the lewisite fragment; hence the arsenic is transferred to this, and the enzyme is freed.

B.A.L. proved outstandingly successful, even when the application was delayed until erythema and oedema had developed; its early application to eyes contaminated with a droplet of lewisite prevented the otherwise inevitable loss of sight. The fact that B.A.L. reverses the development of a pathological condition which has already started is of much theoretical importance. It is to be noted that B.A.L. reverses the poisoning by lewisite of several -SH enzymes other than the pyruvate oxidase system, but most of these have their activity restored also by monothiols; the pyruvate oxidase system is exceptional in needing a dithiol.

Very favourable results have been obtained with B.A.L. in arsenical dermatitis following arsenical therapy and also in accidental arsenical poisoning; B.A.L. has likewise mitigated the complications of gold therapy. Remarkable cures have been reported in poisoning by corrosive sublimate in man (U.S. workers) and in animals (British and U.S. workers). Most cases of poisoning by mercurials can be saved if treated with B.A.L. within 4 hours.

B.A.L. combines with a number of heavy metals as well as with arsenic, and it has interesting research applications. Unfortunately, it is to some extent toxic, and 4-hourly doses must be restricted in patients to about 3 mg. per kilo. if even minor toxic symptoms, such as nausea, are to be avoided. For intravenous injection a glucoside of B.A.L. (B.A.L. Intrav.) was developed jointly by workers in Cambridge and London (Danielli *et al.*, 1946, 1947); though this could not penetrate skin, it is relatively free from toxic effects and has much promise clinically when certain chemical difficulties have been overcome.

### OTHER INVESTIGATIONS IN CHEMICAL DEFENCE RESEARCH

Dr. Honor B. Fell and Dr. C. B. Allsopp at the Strangeways Research Laboratory, Cambridge, applied the tissue culture technique to studies of the biological action of vesicants. Methods were devised

whereby toxic liquids or vapours could be brought into contact with living cultures under continuous observation on the warm stage of a microscope. A new histological method was developed for identifying mustard gas in cells and tissues, and this made it possible to establish the chemical nature of the intracellular droplets which appeared in tissue culture cells treated with mustard gas. In the investigation of the nitrogen mustards, the interesting phenomenon of detoxification by blood plasma was demonstrated.

The action of mustard gas and related substances on proteins and other tissue constituents was studied by Professor Peters and his colleagues at Oxford, Dr. Malcolm Dixon and his colleagues at Cambridge and Professor A. Wormall and his colleagues at St. Bartholomew's Hospital Medical College, London, and later at Cambridge. To determine where the mustard gas reacts in the body, Professor Wormall and his team used mustard gas containing radioactive sulphur and followed the distribution of the sulphur in the body (see Chapter 9). They also established by this method the combination of mustard gas with plasma and other proteins.

Professor J. Masson Gulland at University College, Nottingham, examined the action of mustard gas on nucleic acids, and Drs. R. A. Gregory and D. A. Smythe at University College, London, tested its effects on gastric secretion.

Dr. Ida Mann and her colleagues, first at the Imperial Cancer Research Fund Laboratories, London, and afterwards at Oxford University, investigated the nature and treatment of the eye lesions produced by vesicants and other chemical warfare agents. Dr. J. M. Robson and his co-workers at Edinburgh University also carried out research on the treatment of eye lesions due to war gases, as well as on the effects of vesicants on chromosomes; further work on methods of mitigating the ophthalmological effects of chemical warfare agents was undertaken by Professor W. J. B. Riddell at Glasgow University. The synthetic mydriatic Dimethylaminoethylbenzilate ethochloride, now marketed as 'Lachesine', was developed by Dr. H. R. Ing in Professor Sir Robert Robinson's laboratory at Oxford, as a substitute for atropine in the treatment of mustard gas eye casualties.

Defence against the possibility of attack by vesicants sprayed from aircraft or released from air-burst weapons necessitated much practical research on the vesicant effects of drops of various sizes, and on the casualty-producing effects of aggregations of such drops, either through their direct contact with the skin or by vapour effects through clothing.

The entry of Japan into the war and the commencement of military operations in Burma and New Guinea raised a new set of problems relating to the possible use by the enemy of mustard gas. In tropical climates, it is difficult, if not impossible, to wear impervious protective clothing, the vesicant action of mustard gas liquid and vapour on hot

and sweating skin is much more severe, and the vapour danger to the lungs is increased. To study these and other questions, two tropical experimental stations, staffed largely from the Ministry of Supply Chemical Defence Experimental Station, were set up—one in North Queensland, the other in South India; experiments were also carried out in Egypt and Palestine by personnel from the Experimental Station.

The physiological and pathological effects of poisoning by hydrogen cyanide, cyanogen chloride and phosgene were studied at the Experimental Station and by extra-mural workers for the Ministry of Supply, including Professor I. de Burgh Daly at Edinburgh University.

In the early days of the war, examination of a captured German respirator disclosed that the absorbent granules had recently been modified and gave increased protection against arsine; it was known also that large quantities of arsenic were being imported into Germany. Although it seemed unlikely that the enemy contemplated an extensive use of this gas, the possibility could not be ignored and, as part of the defensive precautions, an exhaustive study of the physiological and pharmacological effects of arsine, and of methods of treatment of arsine poisoning, was carried out by Professor C. A. Lovatt Evans, Professor G. R. Cameron and Professor J. H. Gaddum at the Experimental Station, and by Professor G. F. Marrian and Dr. G. A. Levvy, at Edinburgh University. Arsine is a systemic poison which is rapidly absorbed from the lungs; it reacts at once with oxyhaemoglobin in the circulating blood and destroys the erythrocytes. Considerable amounts of arsenic reach the tissues before haemolysis occurs, and arsine has a direct toxic action on the liver and spleen. In the initial trials B.A.L. proved unsatisfactory as an immediate remedy, though it has since been shown to be effective against any arsenite formed from arsine. The fact that the addition of arsinised blood to normal blood does not cause change in the normal cells suggested blood transfusion as a method of treatment. Blood transfusion alone, however, was not very successful; better results were obtained by transfusion following bleeding.

Psychological tests of the effects of tear gas and arsenical smokes upon human performance were carried out by workers in the Psychological Laboratory at Cambridge University as part of a larger study of problems of human efficiency under conditions of stress (Mackworth, 1950).

The health of the workers at the various factories where chemical warfare agents were manufactured, charged into weapons, and stored, was closely watched, and much valuable experience was gained in the treatment of the casualties that inevitably occurred amongst those working daily with highly toxic chemicals in bulk. Dr. J. F. Wilkinson, of the Department of Clinical Investigation, University of Manchester,

carried out special clinical and haematological investigations of workers in war gas factories.

Experimental work on the various possibilities of chemical attack which troops might encounter in the field was carried out intensively at the Chemical Defence Experimental Station, with the object of improving the defensive measures available; the collaboration of the medical staff was essential to ascertain the probable effects of such attack on man. Amongst the substances against which defence measures were deemed to be necessary were some organic compounds of phosphorus, which were found to be extremely potent in action, causing a very painful miosis in extremely low concentrations and rapid death in higher, but still comparatively low, concentrations.

Trials in connexion with defence against new chemical agents made continuous demands for test animals, and necessitated enlargement of the experimental animal farm attached to the Chemical Defence Experimental Station. Toxicological work with animals demanded that the subjects should be free from illness or disease, and careful breeding was essential to eliminate chance factors. In this connexion, some research was carried out on lung worm infestation of goats and its treatment with anthelmintics. Research was also carried out on curative measures and protective devices for Service animals, e.g. horses, dogs and carrier pigeons.

The extensive use of smoke by the Armed Forces, and the large-scale smoke screens which were put up in the United Kingdom to screen important areas from aerial observation or bombing, necessitated investigation of the effect of long-continued exposure of man to smoke clouds, and of the effect on animals of grazing on pastures contaminated by smoke-producing substances such as phosphorus.

Experimental work on phosphorus burns and their treatment was carried out at the Chemical Defence Experimental Station by Professor Cameron in collaboration with the Burns Sub-committee of the Medical Research Council's War Wounds Committee (see Chapter 3). Professor Cameron was a member of this sub-committee, and he and some of his colleagues at Porton also took an active part in its programme of research on the effects and treatment of thermal burns.

The Experimental Station was intimately concerned with work on the hazards in armoured fighting vehicles, gun-turrets, and pill-boxes from carbon monoxide and propellent fumes produced by firing weapons from such enclosed places (see Chapter 2). Experiments were carried out at the Experimental Station, at the A.F.V. Gunnery School and on H.M. ships, and improvements in the ventilating systems were recommended and tested. Experiments were also carried out on the ventilation of air-raid shelters, and on air movements on the London Underground Railway system, which at that time was largely used by shelterers.

The Experimental Station collaborated with Professor P. A. Buxton, of the London School of Hygiene and Tropical Medicine, in research on the control of lice, with special reference to the war-time menace of louse-borne typhus. At first, reliance was placed on 'lethane' belts, heavily impregnated with organic thiocyanates, but these proved irritant to white-skinned people. In 1942, when D.D.T. became available in quantity, a dusting powder containing 5 per cent. D.D.T. was developed, and this contributed substantially to the control of typhus in the Middle East and in South East Asia Command. Impregnation of shirts with D.D.T. emulsion, and their re-impregnation in the field, was successfully accomplished later, and it was proved that the continued wearing of the impregnated garments had no deleterious effects on health even when they came into contact with open wounds.

An Entomological Section was set up at the Experimental Station, and the work with D.D.T. was extended to the control of mosquitoes, a problem which had become urgent because of outbreaks of malaria on the Italian front. The apparatus designed for spraying vesicants and for putting up smoke curtains was adapted with successful results to the spraying of mosquitoes with D.D.T. oil emulsion. These sprays were effectively used in Italy, India, Burma and West Africa. Screening smoke generators were adapted to give insecticidal smokes of D.D.T. and benzene hexachloride.

Experiments were later extended to locusts, and other insect pests. In the laboratory dinitro*ortho*cresol (D.N.O.C.) in oil was found to be very toxic to locusts when sprayed on to these insects in flight, and successful small-area attacks were made on swarms in East Africa and in Zululand.

## Publications relating to Chapter 10

Most of the war-time work on chemical defence problems was at the time recorded only in the form of confidential reports to the Government departments concerned. The following publications dealing with some of the studies have since appeared.

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# CHAPTER 11

# THE BIOLOGICAL EFFECTS OF EXPLOSIONS

## I. A Summary of the work carried out for the Ministry of Home Security by Professor S. Zuckerman, C.B., F.R.S., and team in the period 1939-46

### INTRODUCTION

At the outbreak of war the Minister of Home Security, Sir John Anderson, convened a Civil Defence Research Committee under the chairmanship of Dr. E. V. (afterwards Sir Edward) Appleton to advise on the research necessary to obtain a scientific foundation for a civil defence policy. At the same time he established within the Ministry a Research and Experiments Department under the direction of Dr. (afterwards Sir) Reginald Stradling.

Little was known at the time about the casualty-hazards which would be associated with air attacks on civilian populations. The current belief was that, because of the development of bigger bombs, and because of the growth of the air forces, the risks run by civilians were likely to be considerably greater than any that had been experienced in the War of 1914-18. In consequence, extensive preparations were made to deal both with the evacuation of civilians from large centres of population and with the disposal and treatment of fatal and non-fatal air-raid casualties. On the basis of Intelligence reports about the strength of the German Air Force and an exaggerated idea about the wounding power of bombs, it was estimated that casualties were likely to be at the rate of more than 100,000 per week. It was generally assumed that 'blast' would prove to be very lethal, and that 'ground shock' would also be responsible for large numbers of casualties. In addition, rumours which had filtered through from Spain during the Civil War of 1936-8 suggested that small fragments of bomb-cases would be very dangerous wounding agents.

The first experiment of the War of 1939-45 which was designed to discover some of the anti-personnel effects of explosions was made in a test of sectional steel ('Anderson') shelters. It was carried out under the auspices of the Ordnance Board, and the physiological observations (on goats and rats) were supervised by the late Sir Joseph Barcroft. The arrangements were in the hands of the Chemical Defence Research Department (Ministry of Supply), the Medical Research Council, and the R.A.M.C. In this trial it was found that the animals closest to the

explosion suffered intrapulmonary haemorrhages, which were believed to be due to sudden distension of the lung. No attempt was made to correlate the severity of the lesions observed with the blast pressures experienced.

After surveying the available information about the resistance of overground structures and trench shelters to the explosion of bare charges and of bombs, the Civil Defence Research Committee and the Research and Experiments Department of the Ministry of Home Security instituted a series of experiments to establish general laws relating the behaviour of different structures to explosions. The first occasion on which biological observations were made during these trials was in November 1939, when Professor Zuckerman tried to discover whether monkeys in contact with the walls of underground trench shelters were affected by the acceleration imparted to the shelter by the ground shock from a nearby explosion of a 250-lb. light-case bomb buried eleven feet deep. This experiment failed to demonstrate any adverse effects at distances which had previously been regarded as dangerous.

A wider programme of experiments was then arranged to explore the wounding effects of air and underwater blast, of small metallic fragments travelling at high velocity, and of rapid acceleration of the body due to explosions. When, in the summer of 1940, the German Air Force began its bombing attacks on English towns it became possible, through the study of actual incidents, to discover how far experimental observations of wounding power made under laboratory conditions corresponded with the character and circumstances of injury associated with the explosion of bombs. As a result, by the time the heavy attacks on London and on the Midland towns began in the autumn of 1940, a technique had been elaborated for analysing the casualty aspects of an incident, and for standardising the wounding power of bombs of different sizes.

The Medical Research Council were not immediately concerned in the start of this work, but in October 1940, at the request of the Ministry of Home Security, they appointed a Research Committee on Air Raid Casualties to assist in analysing the nature of the injuries produced in bombing incidents of different types.

The increasing amount of experimental and field-work in which Professor Zuckerman and his team became involved called for more assistance, and by 1942 professional staff in the team working with him numbered more than twenty. The research group was first administered as an extra-mural unit by the University of Oxford, but early in 1941 that part of the staff which was engaged in field-work was made part of the establishment of the Ministry of Home Security. As the war drew to a close, and when the laboratory work was being wound up,

the experimental staff was taken over and administered directly by the Ministry of Aircraft Production*.

The organisation of the Oxford Extra-Mural Unit closely followed the expansion of its work. Its nucleus was a small group which studied, both in the laboratory and in field experiments, the biological effects of blast and of high-velocity bomb fragments. Its largest component was a field staff which investigated air-raid incidents and casualties in bombed towns. This formed one part of what became known as the 'Casualty Survey', the other being a small central unit which was responsible for the analysis of the records sent in by the field-workers. The whole unit was serviced by a small secretariat.

Experimental work was pursued in a hut-laboratory erected by the Ministry of Home Security on the site of the present Forestry Department of the University of Oxford, and the central analytical work of the Casualty Survey was carried out in a dwelling-house taken over for the purpose. The central office of the whole unit was in the Agricultural Economics Institute at Oxford. The headquarters of the London section of the Casualty Survey was in Guy's Hospital, and of the Birmingham section in the Regional Headquarters of the Ministry of Home Security. These regional headquarters afforded a base from which air raids were studied in all parts of the country.

The primary link of the Oxford Extra-Mural Unit was with the Research and Experiments Department of the Ministry of Home Security, of which it was in essence an out-station. Through this connexion, the Unit was provided with all the information that was available about the physics of explosions, and about the physical effects and power of different German weapons used against this country. By it the Unit was also furnished with all the necessary facilities and assistance in carrying out its laboratory and field work. As its work progressed, the Unit established connexions with all the Service and Supply Departments, both directly and through various committees.

## EXPERIMENTAL STUDIES

The main objective of the research carried out by the Oxford Extra-mural Unit was the assessment of the anti-personnel effects of weapons.

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* The following were at one time or another members of the Oxford Extra-Mural Unit :—

*Director* Professor S. Zuckerman

| Laboratory | Casualty Survey | | |
|---|---|---|---|
| | *Central* | *London* | *Provinces* |
| Dr. P. L. Krohn | Dr. Pamela Blake | Dr. T. McKeown | Dr. C. C. Spicer |
| Dr. B. Delisle Burns | Dr. J. W. B. Douglas | Dr. J. Bull | Dr. R. Powell |
| Col. Libessart | Dr. M. Grüneberg | Dr. A. Davies | Dr. S. W. M. Whitty |
| Dr. Georges Ungar (*Free French Forces*) | Miss A. M. Vidal Hall | Dr. T. R. C. Frazer | Dr. D. M. L. Doran |
| Dr. C. W. Emmens | | Dr. K. K. Conrad | |
| Miss B. G. Hunt | | Dr. G. E. C. Kennedy | |
| Miss E. M. Alden | | Dr. M. Lubran | |
| Miss P. Batty Shaw | | Dr. Hildred | |
| Captain Fulleringer | | Assisted by 17 field workers | |

This task was frequently interrupted by short-term problems of more immediate operational importance, where a rapid approximate solution was often preferable to a thorough but delayed analysis. The urgent need for answers to questions on subjects which, practically speaking, had never before been scientifically studied also made it essential to bear in mind, whatever the problem under investigation, that a wider field of careful observation was always more valuable than a more accurate and better defined, but more limited, inquiry. Consequently, the experimental work outlined below was not always as complete as would have been the case under less pressing conditions. From the point of view of the practical use of the information obtained, this drawback was more than offset in the end by the arbitrary 'operational factors' which inevitably colour most activities in war, and because of which an exact statement, for example, of the blast pressure at which a certain injury could be expected to occur, was, in the interests of safety, and depending on circumstances, either arbitrarily multiplied or divided by two or three by the 'user' of the information.

Although several diverse research projects were usually being examined at the same time, the summary of the work given below has intentionally avoided the historical approach in order to present each project separately.

### THE WOUNDING MECHANISM OF SMALL HIGH VELOCITY MISSILES

Surgical experience during the War of 1914-18, and during the Spanish Civil War, had left the impression that small irregular fragments, travelling at high velocity, frequently caused wounds which were unexpectedly severe.

It had been suggested (Wilson, 1940) that the disproportion between size of wound and size of high-velocity missile might be due to the irregular shape of splinters and to their rotation. This explanation seemed inadequate and it was therefore proposed (Zuckerman, 1940) that a more reasonable interpretation might lie along the lines suggested by Cranz and Becker (1921) in their analysis of the effects of high-velocity missiles in soft media. If the physical explanations of Cranz and Becker were applicable to splinter wounds in flesh, it would follow that the destructive effect of a small splinter is due to violent motion imparted to the soft medium through which it passes. The tissue moves away from the track of the missile and an effect similar to that of an internal explosion is produced.

Experiments were therefore designed to test this hypothesis (Black, Burns and Zuckerman, 1941). The experiments were carried out on rabbits and on blocks of 20 per cent. and 5 per cent. gelatine. The former dilution corresponds to the dilution of protein in the body.

A gun was constructed which fired a $\frac{3}{32}$ in. steel ball weighing 53 mg. at velocities up to about 1,000 m. per second. The choice of this standard missile was to some extent arbitrary. The projectile corresponds in weight to a very large proportion of the splinters into which a bomb-case or shell-case fragments.

The velocity of each shot was measured by Boys' spark photography method. The missile cuts a wire forming part of an electrical circuit and, through a relay, discharges a condenser across a spark gap. By using 10,000 volts and an air spark-gap, sufficient actinic light is obtained from an 'exposure' of less than one microsecond to throw a shadow of the missile and target upon photographic paper. The impact and residual velocities of the missile are calculated from the angle between the sound waves which are thrown off by the missile, and which are photographed.

It was subsequently found that the velocities measured by spark photography of the bow wave are about 10 per cent. too low. Consequently, in later work a different method of velocity measurement was used.

By varying the interval between the impact of the missile on the target and the cutting of the wire it is possible to obtain shadowgraphs of the target at varying times after it is hit. Using identical targets for successive shots, the changes which take place in a target during the fraction of a second after it is struck, were photographed. Later, an apparatus was constructed to take successive pictures of a single shot into one target. This provided a cinematograph record of the target immediately after impact.

It was found that as soon as the ball enters the 20 per cent. gelatine target, a 'tail splash' develops on the entry side. This increases in size while the ball traverses the block. The emerging ball pushes before it a head-cone of gelatine, which it ultimately leaves. This is the only distortion which occurs during the few microseconds taken by the ball to pass through the target. Immediately after complete perforation, the block of gelatine undergoes considerable expansion, until it becomes some three to four times its original volume. In spite of this distortion, the blocks return to their original size and shape. The only permanent visible effect of the shot is a small thread-like track which is similar to that caused by pushing a needle through the block. Occasionally a few small bubbles of air and small radial fractures may be seen in the track. Experiments with blocks of 5 per cent. gelatine gave the same result.

Shadowgraphs of the hind limb of a rabbit immediately before and 550 microseconds after the impact of the steel ball showed the same type of distortion as the gelatine blocks. Similar shadowgraphs of the hind limb of a rabbit were also taken with the thigh muscles bound in four layers of surgical tape. The velocity of the projectile was of the same order as that of the projectiles in the previous experiments. It

was found that the tape binding considerably reduced the distortion of the limb. Later work in America (Harvey, Butler, McMillen and Puckett, 1945) showed that although the distortion in the strapped limb is reduced, the amount of damage to the muscle is increased.

The changes which occur in the gelatine blocks are probably due to the formation, with explosive violence, of a cavity within the blocks. As the high-velocity missile passes through the block, it imparts violent motion to the particles in its track, and these fly off radially, imparting their momentum in turn to further particles. In this way a central cavity, the pressure of which is presumably sub-atmospheric, is formed within the target. It can be estimated from the series of tests on the 4 cm. × 4 cm. × 5 cm. gelatine blocks that, 800 microseconds after impact, the gelatine is distributed in a peripheral layer averaging about 0·5 cm. thick, which surrounds a central cavity approximately 5 cm. in diameter. The instantaneous stresses imposed on the gelatine when struck must be large compared with those that it would be able to resist over a longer period. Nevertheless, it is surprising that there is so little evidence of damage in the gelatine blocks when the cycle of distortion is complete.

The fact that the shadowgraphs of animal limbs are essentially similar to those of the gelatine blocks suggests that the same changes occur in human tissues which are traversed by high-velocity missiles. At the height of the deformation, which occurs after the missile has left the part, the tissues must be stretched around a central cavity of considerable dimensions. Under such conditions, it is obvious that structures at great distances from the track of the projectile can suffer damage. This explains the common clinical observation, which has also been confirmed experimentally, that the minute puncture holes caused by small bomb splinters striking the skin, are often the only external sign of considerable internal injury. Experiments with rubber-coated cylindrical blocks of gelatine also show only minute punctures in the rubber covering, despite the momentary gross distortion of the contents. On the other hand, when the steel ball is fired with high velocity at the skinned limb of a dead rabbit, or a slab of meat, a considerable crater is formed in the flesh on the entry side, and the superficial destruction is much greater than in a corresponding part covered by skin.

The explosive character of the forces set up by the high-velocity ball in its passage is also manifested by the comminuted fractures that may occur in the femur of a rabbit even when the path of the projectile lies more than 1 cm. from the bone. In the same way heavy glass plates placed in contact with the gelatine targets, and 2 cm. from the track of the ball, are shattered.

In contrast to bone, highly elastic structures such as arteries, veins and nerves are liable to escape injury in wounds caused by high-velocity missiles. Thus post-mortem examinations of wounded animals show

that large vessels and nerves may run intact through regions in which muscle and smaller vessels are considerably damaged.

Experiments were carried out to discover whether a large blood vessel will be torn when a high-velocity steel ball passes close enough for the vessel to be within the ensuing zone of cavitation. It proved impossible to break the artery by shots which passed as close as ½ mm. from its walls. The shot which finally broke the artery passed right through it.

Although the larger nerve trunks appear to remain anatomically intact in high-velocity wounds, it should be remembered that they have momentarily undergone considerable stretching around the cavity caused by the missile. This stretching may be the cause of reported cases of transient paralysis and analgesia following bomb splinter wounds, for it is known that a nerve can lose its conducting properties for some time after such distortion.

American investigators have confirmed many of the conclusions which were reported in the early work summarised above (Butler, Puckett, Harvey and McMillen, 1945; Harvey, Butler, McMillen and Puckett, 1945; Harvey, Korr, Oster and McMillen, 1947; Harvey and McMillen, 1947; Harvey, Whiteley, Grundfest and McMillen, 1946; McMillen and Harvey, 1946; Puckett, McElroy and Harvey, 1946).

### THE ASSESSMENT OF THE WOUNDING POWER OF SMALL FRAGMENTS

Soon after these studies on the wounding mechanism of high-velocity small fragments were started, the Ordnance Board asked for estimates of the wounding power of the smaller fragments thrown off from an exploding bomb or shell, the information being required for comparative assessments of the anti-personnel effects of different exploding missiles.

The best biological data to use in answering a question of this kind would be records of actual wounds in which the size of the fragment concerned was known, and in which enough was also known of the circumstances of injury to determine the striking velocity of the fragment. Other information that would be necessary is the relative contribution made to total casualties by fragments weighing 1 g. or less. Such data are non-existent, and the problem had to be investigated experimentally in the following steps: (*a*) the definition of a hospitalising wound; (*b*) the determination of the striking velocity of a standard missile necessary to cause such wounds in different parts of the body; (*c*) the translation of such standard velocities into corresponding splinter velocities; (*d*) the estimation of the mean projected vulnerable area of the body; (*e*) the estimation of the depth of penetration into wood and telephone directories equivalent to a hospitalising wound; (*f*) the assessment of the anti-personnel power of an exploding projectile from data about the character of its fragmentation and about the deceleration of its fragments in flight.

If the analysis had been pursued from the point of view of the definition of the least severe types of wound to which the first-aid worker or surgeon might have to pay attention, one set of standards would have been postulated. Since it was more important to define criteria of incapacitation from the operational point of view, it seemed wiser to take as standards wounds which would without question necessitate medical attention. The adoption of this standard does not imply that a man receiving such a wound would always be put out of action immediately. Many cases are on record of men continuing with very severe injuries. The term does imply, however, that sooner or later the casualty would be out of action for a period in which skilled medical attention would be necessary.

The arbitrary concept of a hospitalising wound that was adopted had to be further defined in terms of arbitrary criteria of penetration into different parts of the body. This having been done, experiment provided general equations relating the mass and velocity of fragments with critical penetration. In a series of further steps, probit curves were determined for incapacitation of the whole body as a target. These curves (unpublished) provided the basis for calculating the relative wounding power of different exploding missiles, a method having been determined for stating the answers in terms of a standard.

This work was completed in 1942. Probably because of the arbitrary nature of certain of the assumptions which had to be made at the start, and which would still need to be made if the work were repeated, it still remains the only completed experimental work that is available for defining the comparative wounding power of exploding missiles—in spite of considerable further experimentation and field observation carried out both by the Oxford Extra-mural Unit and by American workers.

### PROTECTION OF PERSONNEL AGAINST FRAGMENTS

When the question of body-armour for ground forces and for A.R.P. personnel was considered during the early part of the war, the estimates of the expected saving in casualties, by the comparatively small weight of armour which was then regarded as permissible, were disappointing. A report by the Body Protection Committee of the Medical Research Council (1941, unpublished) recommended a type of steel body armour weighing 2 lb. 12 oz. A number of such suits were manufactured and tested but they were not issued to the Forces. The arguments used to support the adoption of body protection for troops depended on three groups of observations:

1. Data regarding casualties in the field, giving the relative incidence of wounds in different parts of the body and the expected mortality from such wounds.

2. A study of a selected number of thoracic wounds from the point of view of the missiles causing them and the depth of their penetration.

3. An experimental study of the actual penetration of missiles into tissues and into various types of protecting material.

It was argued from the medical data that, owing to the high mortality of thoracic wounds and abdominal wounds, it is most important to provide protection for these parts of the body. From the nature of the wounds it was argued further that most of the non-fatal casualties from such wounds are caused by projectiles penetrating less than half-way into the thoracic cage from front to back. The report concluded that the proposed armour would prevent such casualties and reduce total casualties by at least 5 per cent.

A preliminary assessment of the efficiency of this armour was made in the course of the work referred to in the preceding section, and it was calculated that it would save only about 2 per cent. of casualties. This estimate was slightly on the low side, partly because it failed to take into account the belly plate and hence under-estimated the area protected by the armour. It also made no allowance for oblique impact of splinters. Further, only a single weapon (the 20-lb. anti-personnel bomb) was considered, whose burst velocity turned out to be much lower than was assumed.

More detailed data about the fragmentation of various bursting projectiles later became available, and a reassessment of the armour by the Oxford Extra-mural Unit showed that the total saving in casualties, including fatal casualties, would be about 2·6 per cent. of all battle casualties. The difference between the estimate of 5 per cent. given by the M.R.C. Committee's report and the value of 2·6 per cent. derived in the Oxford Unit's second study arose primarily because chest casualties were classed in the former as a separate group, whereas in fact a considerable number of men would be hit simultaneously in the chest and elsewhere. In any event, both estimates were too low to encourage interest in this form of protection against wounds in ground troops, although in 1944 a type of body armour was successfully adopted by the U.S. Strategic Air Forces.

## THE PHYSIOLOGICAL EFFECTS OF BLAST

To a medical officer of the War of 1914–18, blast was something that blew a man to pieces or threw him violently. The clinical literature of that period contains practically no reference to the fact that blast can directly cause injuries in the thorax and abdomen without surface wounds. Numerous observers in the Spanish Civil War reported, however, that the blast from bomb explosions could kill at a great distance from the burst. People were picked up dead without any external injury and usually showed blood-stained froth in the mouth and nose. These reports greatly exaggerated the danger of blast and the distances at which it can cause casualties; but experience in this

country has confirmed the fact that blast can hurt without either blowing a man to pieces or throwing him to the ground.

Few experimental observations on the effects of blast were available at the start of the recent war. The most important work had been done by Hooker (1924) who, in the course of an experimental study of the shock produced by charges of T.N.T. and gun-blast, noted that bruising and occasionally rupture of the lungs was 'the single gross lesion found post-mortem' in animals which had been exposed to air concussion due to gun-blast or high explosive. Hooker also found that disturbances of respiration were frequent, and that they set in at variable times after the explosion. Some animals died as a result of being exposed; others recovered immediately. Physiological studies carried out in England in connexion with official tests of sectional steel shelters had shown that similar lesions occurred in the lungs of animals exposed to only the blast of a 500-lb. medium case bomb.

When a bomb detonates, the solid explosive is converted into gases which initially are confined in the casing at a pressure that has been variously estimated as between 100 and 650 tons per sq. in. As a result of this pressure, the casing is blown to pieces, and the gases escape and by their expansion produce a blast wave in the surrounding air. The blast wave is a single pulse of increased pressure followed by a phase of suction, and in general form is similar to a single pulse of a large amplitude sound wave. The wave moves extremely rapidly, much more rapidly than sound close to the explosion, and, in the case of a medium-sized bomb, falling to the velocity of sound (1,120 ft. per second) at about 200 ft. The total duration of the whole wave at any given point within 200 ft. of an explosion is very brief. Thus at 30 ft. from a 70 lb. charge the pressure component lasts about 5, and the suction component 30 milliseconds. The duration of the pressure component increases progressively with increasing distance from the charge, but the suction component, which generally lasts three to five times as long, remains more or less constant. It should be noted that the velocity and duration of the pressure wave at any given point are such that a body as large as a human being would certainly be completely immersed for an instant in a wave of almost uniformly raised pressure.

The maximum pressure of the wave is highest in the region of the explosion, and the pressure at first falls rapidly the further the wave moves from the source of the explosion. In the case of a 70-lb. charge the pressure falls approximately as follows: 14 ft., 110 lb.; 18 ft., 60 lb.; 30 ft., 15 lb.; 50 ft., 6 lb. These figures represent hydrostatic pressure in excess of normal atmospheric pressure, which is approximately 15 lb. per sq. in.

Any surface facing an explosion will be subjected not only to this excess hydrostatic pressure but also to pressure due to air movement immediately behind the shock-front of the blast wave. Close to an

explosion this pressure may be as great as, or greater than, the hydrostatic pressure of the shock-front, but further from the bomb the pressure effect of this air movement is of little importance; it is negligible for hydrostatic pressures less than 5 lb. per sq. in.

The suction component of the blast wave is always much weaker than the pressure component, and in no case can it ever be greater than 15 lb. per sq. in., since this corresponds to a perfect vacuum.

The magnitudes of the pressure and suction components of a blast wave, and the time they last, are directly correlated with the amount of explosive and are much higher for larger than for smaller amounts. If a given positive pressure is caused by a given amount of explosive at a given distance, the same pressure will be experienced at twice that distance only when the amount of explosive is increased eight times.

All things in the immediate neighbourhood of an explosion thus first experience a violently increased pressure, which may tear them to pieces and blow them far from the scene of the explosion, or affect them directly without doing either of these things. Whether or not an object is shattered by, and blown in the direction of, the pressure wave, it may later be pulled towards the centre of the explosion by the backward movement of air associated with the weaker suction wave, because of the longer time for which this acts.

It should be noted that close to the point of an explosion the advancing wave's front is uneven, so that objects at equally close distances to the point of detonation may be exposed to different pressures. Further away from the explosion the blast wave becomes more even.

The first experiments carried out by Professor Zuckerman and his team were designed to discover how blast produces lesions in the lungs and other organs. In these experiments rabbits and pigeons were subjected to the blast produced by the explosion of large gas-filled balloons. Experiments were then undertaken in which laboratory animals of different sizes were exposed to the explosion of bare charges of high explosive. It was found that there was a range of pressure, which varied from species to species, in which all animals were immediately killed, without external injury but often showing blood-stained froth, or blood, in the nose, mouth and upper respiratory passages. Further away, there was a zone of pressure in which animals were found alive immediately after an explosion but usually died within a day; animals in this group might have blood-stained froth in the upper respiratory passages and frequently showed respiratory symptoms.

Still further from the explosion, internal examination of exposed animals showed damage to the thoracic, and occasionally abdominal, organs. Animals exposed beyond this zone of pressure exhibited neither external nor internal effects of the explosion. Detailed descriptions of the damage to the lungs and other viscera found at post-mortem have been given in various reports (Zuckerman, 1940, 1941).

At the time of these experiments the view was sometimes expressed that blast caused lesions in the lungs by 'forcing its way' down the trachea. The results of the early experiments of the Oxford Extramural Unit did not confirm this view. They showed that:

1. When animals are exposed sideways and close to small explosions, the lesions are unilateral and on the side facing the explosion. When the animals are placed further from the charge the lesions are bilateral.

2. The disposition of lesions in the part of the lungs filling the costomediastinal and phrenico-costal sinuses suggests that they are due to an external 'blow'.

3. Lesions occur not only in the lungs but also in abdominal and other organs.

4. Animals exposed close to a small explosion with their trunks clothed in thick sponge rubber suffer less severely than controls. Animals exposed near the explosion with only one side of the trunk covered in rubber, and with the covered side facing the explosion, suffer no injury or only very slight injury to the lungs. When exposed with the uncovered side to the explosion, they suffer severe damage to the lung of that side and less severe damage to the lung of the opposite side.

5. Rabbits with all but their heads enclosed in steel cylinders do not sustain pulmonary lesions when exposed head-on near large charges.

It can be safely concluded, therefore, that thoracic and abdominal lesions resulting from blast are not due to either pressure or suction components of the wave acting through the upper respiratory passage, but that blast exercises its damaging effects through the surface of the body.

The suction component appears to have little or no effect in the production of lesions. Thus in the experiments referred to above, in which animals were exposed sideways and close to small explosions, the suction component was experienced all round the body, while the far side was shielded from the pressure component by the near side, which received all the injury. In another set of experiments, animals were exposed to a shock wave produced in such a way that there was no following suction component. Typical blast lesions were nevertheless caused. It is thus clear that the thoracic and abdominal lesions resulting from blast are due to the impact of the pressure component on the body wall. The experiments that have been carried out do not, however, exclude the possibility that the lesions caused by the pressure component may be increased as a result of the body wall being pulled outwards by the suction component. The lung lesions are mainly due to the severe blow to the thorax given by the impact of the shock-front. Some of the energy is transmitted through the body, and in the boundary zones between tissues and air, i.e. between acoustically different media, the tissues are torn. This is why gas-containing organs are so much more vulnerable to blast than solid organs.

Closure of the glottis is of no importance in the causation of the lesions. The latent period between stimulation of the animal by the arrival of the blast wave and closure of the glottis can hardly be less than 25 milliseconds. The shock wave would in fact have passed long before the vocal cords could begin to close. It also seems immaterial whether the mouth is open or closed during an explosion, since no appreciable amount of air could travel up or down the trachea in the time intervals involved.

Studies were carried out later to investigate more closely the detailed physiological effects of blast (Krohn, Whitteridge and Zuckerman, 1942). Electrocardiographic records showed that there was no lack of co-ordination of the heart beat, although anaesthetised animals exposed to pressures high enough to cause immediate death might show a slowing of the heart-rate by 60-70 per cent. and a diminution in the amplitude of the record. The electrocardiographs of animals surviving exposure to high pressures might show evidence of a transitory phase of anoxaemia.

Animals exposed to blast showed an immediate fall in arterial blood-pressure, which in extent and duration was related to the peak blast pressure experienced. There was also a slight maintained fall in venous pressure, as observed by Hooker. These 'shock' symptoms are not due to vagal inhibition. The changes in the systemic blood-pressure can be explained as being chiefly secondary to changes in the pulmonary blood-flow.

There was usually a prolonged and great increase in the respiratory rate of rabbits surviving exposure to blast. This appeared to be due to stimulation of 'deflation endings' and increased sensitivity of 'stretch endings' to expansion of the lung, and not to chemical changes affecting the respiratory centre or to any direct effect of blast on the medulla.

Many of these observations have since been corroborated by Clemedson (1949), who has carried out an extensive study of air-blast injuries in the rabbit. He has established the occurrence of 'traumatic emphysema' after blast, and has shown that the increase in the weight of a blasted lung is due to a combination of haemorrhage and oedema, the latter being an unimportant factor. Another interesting observation is that the 'rib markings' on a blasted lung correspond to the intercostal spaces and not the ribs, and it is suggested that they are due not to the sudden impact of the ribs on the lungs, but to extension-strain forces caused by a sudden compression wave propagated through the animal. Clemedson also confirms that heart action is less sensitive to blast than respiration, but he holds that slowing of the heart-rate is dependent on intact vagi, and that it does not occur in atropinised or vagotomised animals. Finally, he confirms that maximum pressure is a more important factor than impulse in the interpretation of the pathological effects of blast.

Since direct observation of the blast pressures likely to cause fatal and non-fatal lesions in man cannot be made, and the information was of considerable importance for certain problems of Civil Defence, the question was investigated indirectly by experiments in animals.

Experiments on mice, guinea-pigs and rabbits showed that the pressure necessary to kill 50 per cent. of animals was related to the $\frac{2}{3}$ power of the body weight. The experimental data for monkeys and goats were consistent with this relation, and further extrapolation to man gave a pressure which accorded with information later provided by the Casualty Survey. Thus the lethal pressure ($P_{50}$) for man was estimated as between 400 and 500 lb. per sq. in., which direct study of certain air-raid incidents showed to be of the right order.

After the pressures required to kill animals had been determined, an attempt was made to find out the pressures necessary to injure those parts of the body which are most sensitive to blast. The ear-drums proved to be the most vulnerable organs. Accurate data, however, were very difficult to obtain, and the pressure which would rupture the human ear-drum in about 50 per cent. of cases could only be roughly estimated as 15 lb. per sq. in.

It was clear that clinically significant damage might be done to the lungs without causing death. An investigation to determine the minimal pressure likely to be injurious to the lungs was carried out, using the same methods and animals as before. The pressure necessary to cause minimal pulmonary damage in man was estimated at 70 lb. per sq. in.

Some preliminary experiments were also made on the effect of repeated exposures to blast pressures. The rather unexpected tentative conclusion was reached that there was little relation between the degree of damage to the lungs and the number of exposures.

A few experiments on the effect of blast in water were also carried out, to test the suggestion that the 50 per cent. fatality peak pressure in underwater blast, unlike that of blast in air, would be the same for all animals, irrespective of size, the heavier chest walls of heavier animals giving no appreciable extra protection against shock waves in water. No confirmation of this suggestion was obtained.

These experimental findings indicate the kind of injuries that are to be expected as a result of the direct action of blast on the body. In air raids, however, the circumstances in which blast acts are very unlike the experimental conditions that have been described. In general it may be said that, of the total number of people injured in air raids, only a small percentage were exposed so close to the burst of a bomb that they would have received direct injuries from the blast wave. Those who were unfortunate enough to be within the danger zone for blast would also have suffered severe injuries due to such other causes as bomb splinters, flying debris, and violent displacement. Internal trauma not dissimilar from that due to pure blast can indeed be caused

by the body's being hurled against solid obstacles such as walls, sides of shelters, etc., or being thrown with considerable force.

### INJURIES DUE TO EARTH SHOCK WAVES

It was clear in the early days of the war that, apart from the direct effects of explosions (blast and fragments), there was serious risk to personnel from falling debris and from violent displacement due to earth shock waves. No information was available which could indicate how important earth movement was as a cause of injury. From a practical point of view, the violent displacement of the earth which occurs when a bomb bursts beneath the surface might be expected to cause injury in two ways. Firstly, people sheltering in slit trenches with their heads resting against the side might receive head injuries caused by the sudden acceleration of the wall. Secondly, people standing up but sheltered from the direct effects of the explosion might be thrown into the air by the earth movement. The latter displacement might be expected to cause fracture of the bones of the heel or the base of the skull.

In order to assess the danger to people sheltering in slit trenches, the experiment briefly mentioned in the introduction to this chapter was carried out. The monkeys used suffered no harm as a result of the explosion, although the earth movement recorded as a result of a similar explosion was the equivalent of about 6 ft. per second and this velocity was acquired with an acceleration of at least 9 g. Close consideration of the disturbance to which the animals were subjected suggested that similar conditions would not have serious effects on human beings.

The Oxford Extra-mural Unit also carried out laboratory experiments to determine whether the movement of a wall which 'instantaneously' reached velocities up to 10 ft. per second would produce concussion in monkeys leaning against it: wall velocities of this order of magnitude are well above those observed for buried 500-lb. G.P. bombs at 25 ft. range. It was found that monkeys subjected to test conditions simulating such movement suffered no serious ill-effects.

The results of the early studies were strongly criticised. It was suggested that human beings could die of fright, and that it was impossible by animal experiment to reproduce the emotional atmosphere of an air raid. These criticisms, which had no factual basis, have been largely vitiated by more recent observations.

### OTHER WORK BY THE OXFORD EXTRA-MURAL UNIT

In addition to the studies which have been summarised above, the Oxford Extra-mural Unit produced numerous reports on civilian air-raid casualties, and a few on surveys of Service battle casualties.

(*Note*: See also the first part of Chapter 18 of the Surgery Volume of this series.)

## II. Research on the Effects of Underwater Explosions (summarised by Professor G. R. Cameron, F.R.S., and Dr. R. H. D. Short)

### INTRODUCTION

After the sinking of their ship, personnel may be exposed to serious injury caused by underwater explosions. Similar hazards are encountered in submarine warfare. At the beginning of the Second World War surprisingly little was known of the nature of these injuries, of the factors which modify them, and of methods of protection. It was soon realised, however, that the chief lethal effect of underwater blast was upon the abdomen, in contrast with airborne blast in which severe lung injury was more often prominent. As the war progressed, detailed accounts of such cases accumulated and some of these have appeared in the medical journals. Experimental work on a variety of laboratory animals was undertaken by a group of investigators in the United Kingdom; their results, too, have been published. British clinical and experimental research on the subject is here summarised and brief reference is made to some relevant Canadian and American studies. (See also the second part of Chapter 18 in the Surgery Volume of this series.)

### OBSERVATIONS IN MAN

*Clinical Features.* Careful study showed that abdominal injury was present in almost all fatal cases and that the incidence of severe lung damage was somewhat less. Indeed, in many cases which came to autopsy lung damage was relatively slight or absent.

On admission to hospital survivors might complain of acute abdominal pain, of having had the sensation of 'a kick in the stomach', often with testicular pain. Sometimes they suffered from numbness or paralysis of the legs (and in a few fatal cases this might have been the cause of drowning), though unconsciousness was rare.

A rapidly developing state of shock, with melaena and early signs of general peritonitis, indicated the urgent need for operation, when single or multiple perforations of the gut were found. Most commonly these were situated in the upper and lower portions of the small intestine, and in the caecum and ascending, transverse and pelvic colons. Perforation of the rectum or duodenum was rare and no case of injury to the stomach seems to have been recorded. As many as eight intestinal perforations have been found in one subject. Even where there was no perforation multiple haemorrhages might be present, most often in the retroperitoneal tissues though commonly associated with large haemorrhages into the peritoneal cavity. Such haemorrhages were also noted in the lower portion of the ileum and in the ascending or transverse colons. These types of severe injury might cause death

at any time within the first week. A striking and significant observation was the rarity of injuries to the solid or fluid-containing abdominal viscera; even when present the injuries to these organs were seldom serious.

In addition to the evidence of abdominal injury, many cases developed chest symptoms, but it was uncommon for serious thoracic injury to occur alone. Chest symptoms included haemoptysis, cyanosis with shallow, grunting respiration, cough and pain in the chest or shoulder (which occurred also in purely abdominal injury). Such symptoms, along with evidence of abdominal injury, were noted especially in patients who died within twenty-four hours of admission to hospital. Death on the twelfth day after blast exposure was commonly associated with bronchopneumonia and pulmonary oedema.

The thoracic lesions resembled those of airborne blast and were mainly multiple, small or massive haemorrhages. These were basal, in the costo-phrenic angle or situated along the lateral margins. They gave rise to bronchial or pleural haemorrhage with collapse of the lung or lobe and subsequent bronchopneumonia. Fat embolism was discovered infrequently. Two cases in which subdural or subarachnoid haemorrhages were striking features have been recorded, but injuries to the brain itself have not occurred. No pathological basis for the testicular pain has been found in man, though experimental studies have shown testicular haemorrhage in a few animals.

The milder types of injury recovered uneventfully and it is probable that permanent injury is rare (Wakeley, 1943; Cameron, Short and Wakeley, 1943).

*Treatment.* The principles of treatment have been well discussed by Williams (1944). In the early stages close observation is essential until the necessity for laparotomy has been decided. Abdominal distension requires very careful use of enemata. Caution in the choice of anaesthetic and in the use of transfusions is also necessary when chest complications are present. Nursing in the half-sitting position is recommended, with continuous oxygen for severe lung cases. Sedatives must be used with care, and heat applied to the abdomen is useful where no sedative can safely be given. Following perforation or peritoneal haemorrhage sulphonamides (especially sulphadiazine) and penicillin are important adjuvants. No patient who has been complaining of abdominal pain or melaena should be discharged for at least ten days, owing to the risk of late complications. Attention to bladder function is very important.

*The Danger Zone of an Underwater Explosion.* Except as showing that it is safest to be far away from the explosion little or no importance attaches to survivors' estimates of their distance from the explosive focus. The size of the charge, its distance below the surface of the sea, and the depth of the sea floor can rarely be recorded at the time of the

episode, and it is these factors which influence the severity of the injury. It may indeed be surmised that apparently anomalous effects of blast would be explained if the value of each of these factors were known.

*Protection against Underwater Blast.* In this field of inquiry much importance attaches to the survivor's statement of his position in the water at the moment of blasting. Survivors who had been floating belly downwards or with their abdomens completely immersed often showed more serious effects than those who had been floating on their backs. A striking illustration is afforded by an officer whose wrist watch and cigarette lighter were completely flattened by blast whilst he floated on his back (Webster, Ross and Alford, 1943). He survived and was discharged from hospital in a fortnight, although his captain, who had been swimming belly downwards beside him, perished.

Floating wreckage may enable men to pull themselves out of the water and thus to escape serious injury. The Kapok Life Jacket to cover chest and abdomen affords good protection. In fifteen survivors who wore such jackets to cover the chest, lung injury was slight, although abdominal injuries were serious (Webster *et al.*, 1943).

## EXPERIMENTAL STUDIES

In September 1941, a team of investigators from the Royal Naval Hospital at Haslar and the Chemical Defence Experimental Station, Porton, began a series of experiments in which various species of animals were exposed at distances up to 100 yards from the explosion of a 320-lb. depth charge of T.N.T. suspended 48 ft. below the surface of the sea, which was 90 ft. deep in the locality of the experiment (Cameron, Short and Wakeley, 1942; Williams, 1942). Some of the animals were protected by 'sorbo' rubber shields covering the chest and abdomen. The most severe injuries occurred within a radius of 40 yds., eleven of thirteen animals being killed outright, but immediate death was not invariably accompanied by lung haemorrhage. On the other hand, lung haemorrhage occurred in animals as far distant as 100 yds. The right lung was more often affected than the left, particularly in the upper lobe and margins. Histological examination did not, however, reveal the degree of tearing which would have been expected from the severity of the haemorrhage, and it was concluded that blood cells were forced from the capillaries in some unknown fashion.

Rents were found in the gut, associated with groups of mucosal haemorrhages which were often strikingly arranged in bands of varying widths, though unrelated to any anatomical structure. In another series of experiments, in which goats and monkeys were used, lung lesions were found to be reduced in severity when the abdomen alone was immersed (Cameron, Short and Wakeley, 1943). The general distribution of the gut lesions suggested that they were related (in part, at

any rate) to the presence of intestinal gas. However, the small intestine with little gas in the goat often showed severe lesions, whilst the large gas-containing stomach showed few lesions. In one monkey, in which a bubble of air had been deliberately introduced into the urinary bladder which was then filled with saline, a localised haemorrhage was found at the site of the air bubble. Haemorrhage was slight or absent when the bladder was filled with saline only. Similar results have also been obtained, although the technique was different, by American workers (Greaves, Draeger, Brines, Shaver and Corey, 1943). As with human subjects, experimental animals exposed to underwater explosions seldom showed lesions of the solid viscera and somatic structures. The theoretical basis for this difference is discussed by Williams (1942, 1944) and Wakeley (1943) in this country, and by Greaves *et al.* (1943) in America. Other investigators have described air embolism and emphasise the importance of air embolism in the coronary vessels (Gouze and Hayter, 1944; Carlton, Rasmussen and Adams, 1945).

SUMMARY

The war-time contribution to the medical study of underwater explosions was of two kinds: (1) the definition of clinical features and their associated pathology; this formed the basis of directives for treatment and prevention; (2) an experimental investigation of factors concerned in underwater blast and the time sequence of pathological changes. Some idea of the fundamental processes concerned in the structural damage caused by such explosions was obtained in this way but a great deal more requires to be done before a precise theory of explosion injury can be put forward.

## Publications relating to Chapter 11

### (1) REPORTS BY MEMBERS OF THE OXFORD EXTRA-MURAL UNIT AND COLLABORATORS

Most of the reports of the Oxford Extra-Mural Unit were submitted confidentially to the Ministry of Home Security and other Government departments. The references given below are confined to work which has been published.

BLACK, A. N., BURNS, B. D. and ZUCKERMAN, S.—
An experimental study of the wounding mechanism of high-velocity missiles. *Brit. med. J.*, 1941, **ii**, 872.

KROHN, P. L., WHITTERIDGE, D. and ZUCKERMAN, S.—
Physiological effects of blast. *Lancet*, 1942, **i**, 252.

UNGAR, G.—
Effects of ascorbic acid on the survival of traumatised animals. *Nature, Lond.*, 1942, **149**, 637.
Experimental traumatic 'shock'. *Lancet*, 1943, **i**, 421.
The effect of trauma on the release of histamine from blood cells *in vitro*. *J. Physiol.*, 1943, **102**, 19P.
The inhibition of histamine release by a pituitary-adrenal mechanism. Ibid. 1944, **103**, 333.

ZUCKERMAN, S.—
Wounds from bomb fragments. (Correspondence.) *Brit. med. J.*, 1940, **ii**, 131.
Experimental study of blast injuries to the lungs. *Lancet*, 1940, **ii**, 219.
Blast injury to lung. (Correspondence.) *Brit. med. J.*, 1941, **i**, 645.
The problem of blast injuries. *Proc. Roy. Soc. Med.*, 1941, **34**, 171.
Ocular injuries resulting from the war. *Trans. Ophthal. Soc. U.K.*, 1941, **61**, 45.

## (2) PUBLICATIONS BY OTHER WORKERS MENTIONED IN PART I OF THIS CHAPTER

BUTLER, E. G., PUCKETT, W. O., HARVEY, E. N. and MCMILLEN, J. H.—
Experiments on head wounding by high velocity missiles. *J. Neurosurg.*, 1945, **2**, 358.
CLEMEDSON, C. J.—
An experimental study of air-blast injuries. *Acta physiol. scand.*, 1949, **18**, Suppl. 61.
CRANZ, C. and BECKER, K.—
*Handbook of Ballistics*. Vol. 1. Translated from the 2nd German Edition. London: H.M. Stationery Office, 1921.
HARVEY, E. N., BUTLER, E. G., MCMILLEN, J. H. and PUCKETT, W. O.—
Mechanism of wounding. *War Medicine*, 1945, **8**, 91.
HARVEY, E. N., KORR, I. M., OSTER, G. and MCMILLEN, J. H.—
Secondary damage in wounding due to pressure changes accompanying the passage of high velocity missiles. *Surgery*, 1947, **21**, 218.
HARVEY, E. N. and MCMILLEN, J. H.—
An experimental study of shock waves resulting from impact of high velocity missiles on animal tissues. *J. exp. Med.*, 1947, **85**, 321.
HARVEY, E. N., WHITELEY, A. H., GRUNDFEST, H. and MCMILLEN, J. H.—
Piezo-electric crystal measurements of pressure changes in the abdomen of deeply anaesthetised animals during the passage of high velocity missiles. *Milit. Surg.*, 1946, **98**, No. 6.
HOOKER, D. R.—
Physiological effects of air concussion. *Amer. J. Physiol.*, 1924, **67**, 219.
MCMILLEN, J. H. and HARVEY, E. N.—
A spark shadowgraphic study of body waves in water. *J. appl. Physics.*, 1946, **17**, 541.
PUCKETT, W. O., MCELROY, W. D. and HARVEY, E. N.—
Studies on wounds of the abdomen and thorax produced by high velocity missiles. *Milit. Surg.*, 1946, **98**, No. 5.
WILSON, H. C.—
Wounds from bomb fragments. (Correspondence.) *Brit. med. J.*, 1940, **ii**, 66.

## (3) OTHER RELEVANT PUBLICATIONS (INCLUDING STUDIES OF UNDERWATER BLAST)

CAMERON, G. R., SHORT, R. H. D. and WAKELEY, C. P. G.—
Pathological changes produced in animals by depth charges. *Brit. J. Surg.*, 1942, **30**, 49.
Abdominal injuries due to under-water explosion. Ibid., 1943, **31**, 51.
CARLTON, L. M., JUN., RASMUSSEN, R. A. and ADAMS, W. E.—
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GOUZE, F. J. and HAYTER, R.—
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HADFIELD, G., ROSS, J. M., SWAIN, R. H. A. and DRURY-WHITE, J. M.—
Blast from high explosive. Preliminary report on ten fatal cases. With a note on the identification and estimation of carboxyhaemoglobin in formol-fixed material. *Lancet*, 1940, **ii**, 478.
LATNER, A. L.—
The low-pressure phase of blast. *Lancet*, 1942, **ii**, 303.
TUNBRIDGE, R. E. and WILSON, J. V.—
The pathological and clinical findings in blast injury. *Quart. J. Med.*, 1943, **12**, 169.

WAKELEY, C. P. G.—
Blast injuries. *Glasgow med. J.*, 1943, **139**, 91.
WEBSTER, D. R., ROSS, A. S. and ALFORD, E. L.—
Immersion blast injuries of the abdomen. *Canad. med. Ass. J.*, 1943, **49**, 1.
WILLIAMS, E. R. P.—
Blast effects in warfare. *Brit. J. Surg.*, 1942, **30**, 38.
Problems and treatment of immersion blast in the British Navy. *War Med.*, 1944, **6**, 296.
WILSON, J. V. and TUNBRIDGE, R. E.—
Pathological findings in a series of blast injuries. *Lancet*, 1943, **i**, 257.

# APPENDIX I

# WAR-TIME COMMITTEES OF THE MEDICAL RESEARCH COUNCIL

(*Note:* Certain committees whose work was not directly related to the war effort are omitted from this list. Titles and honours conferred after the end of 1947 are not included.)

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Professor E. C. Dodds, M.V.O., M.D., F.R.C.P., F.R.S.
Surgeon Vice-Admiral Sir Sheldon Dudley, K.C.B., O.B.E., M.D., F.R.C.P., F.R.S., K.H.P.
Professor J. H. Gaddum, Sc.D., M.R.C.S., F.R.S.
Colonel S. P. James, C.S.I., C.M.G., M.D., F.R.S., I.M.S. (*ret.*).
W. H. Kauntze, C.M.G., M.B.E., M.D., F.R.C.P.
H. King, D.Sc., F.R.S.
Lieut. Colonel B. G. Maegraith, M.B., B.Sc., D.Phil., R.A.M.C.
Major General L. T. Poole, D.S.O., M.C., K.H.P., *late* R.A.M.C.
Brigadier J. A. Sinton, V.C., O.B.E., D.Sc., M.B., F.R.S. (I.M.S. *ret.*).

P. G. Stock, C.B., C.B.E., M.B., F.R.C.P.
Air Marshal Sir Harold Whittingham, K.C.B., K.B.E., F.R.C.P., K.H.P., R.A.F.
Professor L. J. Witts, M.D., F.R.C.P.
Major J. W. Howie, M.D., R.A.M.C.
F. Hawking, D.M., D.T.M. (*Secretary*).
Major J. Reid, M.B., M.R.C.P., R.A.M.C. (*Assistant Secretary*).

*Additional Members of Sub-Committees*

*Chemistry and Pharmacology*—(*Chairman:* H. King, D.Sc., F.R.S.; *Secretary:* F. Hawking, D.M., D.T.M.)
S. Ellingworth.
D. Ll. Hammick.
Professor E. J. King, Ph.D.
Surgeon Commander G. Southwell-Sander, M.B., D.P.H., R.N.

*Drug Prophylaxis*—(*Chairman:* Major General Sir Alexander Biggam, K.B.E., C.B., M.D., F.R.C.P., *late* R.A.M.C.; *Secretary:* F. Hawking, D.M., D.T.M.)
W. D. Nicol, M.B., F.R.C.P.
Colonel C. S. Ryles, R.A.M.C.
Surgeon Commander G. Southwell-Sander, M.B., D.P.H., R.N.
P. G. Shute.

*Therapy*—(*Chairman:* Major General Sir Alexander Biggam, K.B.E., C.B., M.D., F.R.C.P., *late* R.A.M.C.; *Secretary:* F. Hawking, D.M., D.T.M.; *Assistant Secretary:* Major J. Reid, M.B., M.R.C.P.)
Surgeon Commander G. Southwell-Sander, M.B., D.P.H., R.N.

## MEDICAL MYCOLOGY

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Professor L. P. Garrod, M.D., F.R.C.P.
Sir Archibald Gray, M.D., F.R.C.P., F.R.C.S.
P. H. Gregory, D.Sc., Ph.D.
I. Muende, M.B., B.Sc., M.R.C.P.
J. Ramsbottom, O.B.E., D.Sc.
A. H. T. Robb-Smith, M.D.
Professor M. J. Stewart, M.B., F.R.C.P.
Sydney Thomson, M.D., F.R.C.P.
S. P. Wiltshire, D.Sc.
R. St. John-Brooks, M.D. (*Secretary*).

## MILITARY PERSONNEL RESEARCH COMMITTEE

*The Right Hon. Viscount Falmouth (*Chairman*).
Professor F. C. Bartlett, C.B.E., M.A., F.R.S.
Senior Controller M. Baxter-Ellis, C.B.E. (*from November* 1943).
*G. L. Brown, C.B.E., M.Sc., M.B., F.R.S.
Brigadier A. D. Buchanan-Smith (*from May* 1943).
*Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P.
Wing Commander C. E. Chilton, R.A.F. (*April to November* 1941).
*K. J. W. Craik, Ph.D.
Brigadier F. A. E. Crew, M.D., D.Sc., F.R.S., R.A.M.C.
Surgeon Vice Admiral Sir Sheldon Dudley, K.C.B., O.B.E., M.D., F.R.C.P., F.R.S., K.H.P.
Major General A. R. Godwin-Austen, C.B., O.B.E., M.C. (*April* 1943 *to January* 1944).
H. J. Gough, C.B., M.B.E., D.Sc., Ph.D., M.I.Mech.E., F.R.S.
*C. S. Hallpike, M.B., F.R.C.P., F.R.C.S.

* Members of original Body Protection Committee.

Lieut. General Sir Alexander Hood, G.B.E., K.C.B., M.D., F.R.C.P., K.H.P., *late* R.A.M.C.
*The Right Hon. Lord Horder, G.C.V.O., M.D., F.R.C.P.
*Brigadier C. G. Ling, C.B., D.S.O., M.C.
*Sir John H. Parsons, C.B.E., D.Sc., M.B., F.R.C.S., F.R.S.
Major General D. T. Richardson, C.B., M.C., M.B., K.H.S., *late* R.A.M.C.
Major General S. F. Rowell, C.B.E. (*from January* 1944).
*Professor G. I. Taylor, M.C., D.Sc., F.R.S. (*until January* 1943).
*Major General Sir Henry L. Tidy, K.B.E., M.D., F.R.C.P., R.A.M.C.
Wing Commander D. J. Waghorn, A.F.C., R.A.F. (*from November* 1941).
*Kenneth M. Walker, O.B.E., M.B., F.R.C.S.
Chief Controller L. V. L. E. Whately, C.B.E. (*until November* 1943).
Air Marshal Sir Harold Whittingham, K.C.B., K.B.E., F.R.C.P., K.H.P., R.A.F.
*E. A. Carmichael, C.B.E., M.B., F.R.C.P. (*Secretary*).

*Additional Members of Sub-Committees*

*Accidents to Army Vehicles*—(*Chairman:* Professor F. C. Bartlett, C.B.E., M.A., F.R.S.).
Colonel E. R. Cawdron (*until November* 1942).
Lieut. Colonel F. N. Charlton (*from November* 1942).
Major L. Cromwell (*from August to November* 1942).
Professor A. Bradford Hill, D.Sc., Ph.D.
Lieut. Colonel E. V. Hill (*from November* 1943).
Brigadier K. G. McLean (*until November* 1943).
Major W. J. Potter (*until August* 1942).
Lieut. Colonel J. W. A. Stones (*until November* 1943).
F. J. C. Herrald, M.B., M.R.C.P.E. (*Secretary*).

*Air-borne Troops*—(*Chairman:* E. A. Carmichael, C.B.E., M.B., F.R.C.P.; *Secretary:* G. L. Brown, C.B.E., M.Sc., M.B., F.R.S.)
T. Bedford, D.Sc., Ph.D.
Captain W. B. P. Bradish.
Major D. C. Curme.
Brigadier A. A. Eagger, C.B.E., M.B., Ch.B., R.A.M.C. (T.A.)
Captain J. W. Magladery, M.D., R.C.A.M.C. (*from February* 1942).
Sir Edward Penton, K.B.E., B.Sc., F.I.C.
Sir Robert Pickard, D.Sc., F.R.S.
Major M. D. Sieff.
Lieut. Colonel K. B. Smyth.
J. W. Thomas.
B. H. Wilsdon, B.Sc.
Flight Lieutenant B. J. O. Winfield, R.A.F.V.R.
Wing Commander R. H. Winfield, D.F.C., A.F.C., M.B., R.A.F.V.R.

*Armoured Fighting Vehicles*—(*Chairman:* Sir Edward Mellanby, K.C.B., M.D., Sc.D., F.R.C.P., F.R.S.; *Secretary:* E. A. Carmichael, C.B.E., M.B., F.R.C.P.).
T. Bedford, D.Sc., Ph.D.
Brigadier W. M. Blagden (*from July* 1943).
Colonel J. A. M. Bond (*until September* 1941).
Colonel G. W. Busk (*from December* 1942).
Lieut. Colonel A. C. Campbell, R.A.M.C. (*January* 1942 *to October* 1943).
Lieut. Colonel P. J. L. Capon, M.R.C.S., D.P.H., R.A.M.C. (*from October* 1943).
Lieut. Colonel D. H. Carter (*from December* 1943).
Professor I. de Burgh Daly, M.D., F.R.S. (*from March* 1943).
Professor C. A. Lovatt Evans, D.Sc., F.R.C.P., F.R.S.
Brigadier M. L. Formby, M.B., B.Sc., F.R.C.S., R.A.M.C. (T.A.) (*from March* 1942).

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* Members of original Body Protection Committee.

Lieut. Colonel G. Gaisford (*from January* 1945).
Major Sir Arthur Harford, Bt. (*from August* 1942).
Lieut. Colonel R. N. Harding-Newman (*December* 1942 *to October* 1944).
W. J. Mesher (*from December* 1942).
Lieut. Colonel V. R. Paravicini (*from October* 1944).
E. E. Pochin, M.D., F.R.C.P.
Colonel E. McLeod Ross (*from February* 1942).
Colonel D. M. Rycroft.
Brigadier H. A. Sandiford, M.C., M.B., D.P.H., *late* R.A.M.C.
O. M. Solandt, M.D., M.R.C.P.
Colonel C. W. M. Timmis, D.S.O. (*September* 1941 to *December* 1942).
F. A. Vick, Ph.D., F.Inst.P.

*Body Armour and Helmets*—(*Chairman:* Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P.; *Secretary:* E. A. Carmichael, C.B.E., M.B., F.R.C.P.).
Professor J. D. Bernal, D.Sc., F.R.S.
Professor Sir Hugh Cairns, K.B.E., D.M., F.R.C.S. (*since April* 1942).
W. A. Carter.
O. M. Solandt, M.D., M.R.C.P.
Professor S. Zuckerman, C.B., D.Sc., M.D., F.R.S.

*Clothing*—(*Chairman:* The Right Hon. Viscount Falmouth).
H. Bradley, B.Sc., D.I.C. (*from October* 1941).
Commander G. T. Coney, R.N. (*until October* 1941).
Professor C. G. Douglas, C.M.G., M.C., M.D., B.Sc., F.R.S.
R. M. Filmer, M.B.E., B.Sc., F.I.C. (*from October* 1941).
Captain R. Oliver-Bellasis, C.V.O., R.N. (*from October* 1941).
Sir Edward Penton, K.B.E., B.Sc., F.I.C. (*since August* 1941).
Sir Robert Pickard, D.Sc., F.R.S.
Major M. D. Sieff.
J. R. Whinfield (*from March* 1942).
Captain F. S. Wigley.
B. H. Wilsdon, B.Sc.
T. Bedford, D.Sc., Ph.D. (*Secretary*).

*Entomology*—
Professor P. A. Buxton, C.M.G., M.R.C.S., F.R.S. (*Chairman*).
Major W. L. Aylwin (*until April* 1942).
Major General Sir Alexander Biggam, K.B.E., C.B., M.D., F.R.C.P., *late* R.A.M.C.
Sir Rickard Christophers, C.I.E., O.B.E., M.B., F.R.S. I.M.S. (*ret.*) (*from September* 1942).
Professor R. M. Gordon, O.B.E., M.D., Sc.D., F.R.C.P.
Air Commodore T. McClurkin, M.B., D.P.H., R.A.F.
Major K. Mellanby, Ph.D., R.A.M.C.
Professor J. W. Munro, D.F.C., D.Sc. (*from February* 1943).
Major H. I. Pocock (*from April* 1942).
V. B. Wigglesworth, M.D., F.R.S. (*Secretary*).

*Motion Sickness*—(*Chairman:* E. A. Carmichael, C.B.E., M.B., F.R.C.P.; *Secretary:* G. L. Brown, C.B.E., M.Sc., M.B., F.R.S.)
Surgeon Captain R. A. Graff, M.R.C.S., L.R.C.P., R.N.
Brigadier R. J. Napier.
Major H. J. Pocock.
Professor L. J. Witts, M.D., F.R.C.P.

*Rations*—(*Chairman:* E. A. Carmichael, C.B.E., M.B., F.R.C.P.).
Major I. A. Anderson, M.B.E., B.Sc., M.B., R.A.M.C., (T.A.).
Major E. Barnard, C.B.E., D.S.O.
E. B. Hughes, D.Sc.
J. King.
L. H. Lampitt, D.Sc., F.R.I.C.

Professor R. A. McCance, M.D., Ph.D., F.R.C.P.
Wing Commander T. F. Macrae, O.B.E., D.Sc., R.A.F.V.R.
Brian B. Roberts, D.Sc.
Professor B. S. Platt, C.M.G., M.Sc., M.B., Ph.D. (*Secretary*).

*Weapons* (*Biological Assay*)—(*Secretary:* G. L. Brown, C.B.E., M.Sc., M.B., F.R.S.)
Sir Henry H. Dale, O.M., G.B.E., M.D., F.R.C.P., F.R.S. (*Chairman*).
Major W. H. Aylwin (*from November* 1941).
Professor J. D. Bernal, D.Sc., F.R.S.
Major A. J. McAlpine Downie (*from November* 1941).
Surgeon Captain R. A. Graff, M.R.C.S., L.R.C.P., R.N.
Professor C. A. Lovatt Evans, D.Sc., F.R.C.P., F.R.S.
Brigadier J. L. P. Macnair.
A. H. T. Robb-Smith, M.D.
Professor S. Zuckerman, C.B., D.Sc., M.D., F.R.S.

*Vision*—(*Secretary:* E. A. Carmichael, C.B.E., M.B., F.R.C.P.).
Sir John H. Parsons, C.B.E., D.Sc., M.B., F.R.C.S., F.R.S. (*Chairman*).
Lieut. Colonel H. E. C. de Chassiron.
Brigadier Sir Stewart Duke-Elder, K.C.V.O., M.D., Ph.D., F.R.C.S., R.A.M.C.
E. E. Pochin, M.D., F.R.C.P.
Major H. I. Pocock.
F. A. Vick, M.Sc., Ph.D., F.Inst.P.

## NERVE INJURIES

Brigadier G. Riddoch, M.D., F.R.C.P., R.A.M.C. (*Chairman*).
Brigadier W. R. Bristow, M.B., F.R.C.S., R.A.M.C.
G. L. Brown, C.B.E., M.Sc., M.B., F.R.S. (*until May*, 1943).
Brigadier Sir Hugh Cairns, K.B.E., D.M., F.R.C.S., R.A.M.C.
Professor W. E. le Gros Clark, D.Sc., F.R.C.S., F.R.S. (*from November* 1943).
Surgeon Captain M. Critchley, M.D., F.R.C.P., R.N.V.R.
J. G. Greenfield, M.D., B.Sc., F.R.C.P.
Professor G. Jefferson, C.B.E., M.B., F.R.C.S. (*from October* 1943).
Professor J. R. Learmonth, C.B.E., Ch.M., F.R.C.S.E.
Professor H. Platt, M.D., M.S., F.R.C.S.
Professor H. J. Seddon, D.M., F.R.C.S.
Air Vice Marshal Sir Charles P. Symonds, K.B.E., C.B., M.D., F.R.C.P., R.A.F.V.R.
Professor J. Z. Young, M.A., F.R.S.
E. A. Carmichael, C.B.E., M.B., F.R.C.P. (*Secretary until September* 1942).
F. J. C. Herrald, M.B., M.R.C.P.E. (*Secretary from September* 1942).

## NON-IONISING RADIATIONS

Professor H. Hartridge, M.D., D.Sc., F.R.S. (*Chairman*).
P. Bauwens, M.R.C.S., L.R.C.P.
R. B. Bourdillon, C.B.E., M.C., A.F.C., D.M.
Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P.
Professor J. A. Carroll, Ph.D.
J. Guild, F.Inst.P.
Professor F. L. Hopwood, D.Sc.
Professor W. V. Mayneord, D.Sc. (*Secretary*).

## PATULIN CLINICAL TRIALS

Professor H. P. Himsworth, M.D., F.R.C.P. (*Chairman*).
A. J. Amor, M.D., M.Sc.
C. H. Andrewes, M.D., F.R.C.P., F.R.S.
T. E. Cawthorne, F.R.C.S.
Professor M. Greenwood, D.Sc., F.R.C.P., F.R.S.

B. M. Merriman, M.R.C.S., L.R.C.P.
H. J. Parish, M.D., F.R.C.P.E.
Professor H. Raistrick, Sc.D., F.R.S.
W. L. Scott, M.C., M.D.
P. D'Arcy Hart, M.D., F.R.C.P. (*Secretary*).
Mrs. Joan Faulkner, M.B., B.S., D.P.H. (*Assistant Secretary*).

## PENICILLIN CLINICAL TRIALS

Professor H. R. Dean, M.D., F.R.C.P. (*Chairman*).
Professor J. H. Burn, M.D., F.R.S.
A. N. Drury, C.B.E., M.D., F.R.S.
Surgeon Vice Admiral Sir Sheldon Dudley, K.C.B., O.B.E., M.D., F.R.C.P., F.R.S., K.H.P.
Professor Sir Alexander Fleming, M.B., F.R.C.S., F.R.C.P., F.R.S.
Professor Sir Howard Florey, M.B., Ph.D., F.R.S.
Sir Archibald Gray, C.B.E., M.D., F.R.C.P., F.R.C.S.
C. H. Hampshire, M.B., B.Sc., Ph.C., F.R.I.C.
Sir Percival Hartley, C.B.E., M.C., D.Sc., F.R.S.
R. Vaughan Hudson, F.R.C.S.
Air Vice Marshal G. L. Keynes, M.D., F.R.C.S., R.A.F.V.R.
Professor J. R. Learmonth, C.B.E., Ch.M., F.R.C.S.E.
Major General L. T. Poole, D.S.O., M.C., K.H.P., *late* R.A.M.C.
C. M. Scott, D.Sc., M.B.
J. W. Trevan, M.B., B.Sc., F.R.C.S., F.R.S.
Professor R. V. Christie, D.Sc., M.D., F.R.C.P. (*Secretary*).
Professor L. P. Garrod, M.D., F.R.C.P. (*Assistant Secretary*).

## PENICILLIN SYNTHESIS

Professor Sir Robert Robinson, D.Sc., F.R.S. (*Chairman*).
W. Bradley, M.Sc., Ph.D.
H. C. Carrington, M.Sc., Ph.D.
E. Chain, Ph.D., F.R.S.
A. H. Cook, B.Sc., Ph.D.
C. R. Harington, Ph.D., F.R.S.
Professor I. M. Heilbron, D.S.O., D.Sc., F.R.S.
A. Mortimer, O.B.E.
G. Newbury, B.Sc., F.R.I.C.
D. A. Peak, M.Sc., D.Phil.
F. A. Robinson, M.Sc., F.R.I.C.
W. A. Sexton, B.Sc., Ph.D., F.R.I.C.
S. Smith, B.Sc., Ph.D., F.R.I.C.
Professor A. R. Todd, B.Sc., Ph.D., F.R.S.
H. King, D.Sc., F.R.S. (*Secretary*).

## PREVENTIVE MEDICINE

Sir W. Wilson Jameson, K.C.B., M.D., F.R.C.P., D.P.H. (*Chairman*).
J. A. H. Brincker, M.B., D.P.H., F.R.I.C.
Sir W. Allen Daley, M.D., F.R.C.P., D.P.H.
J. Fenton, C.B.E., M.D., M.R.C.P., D.P.H.
J. Ferguson, C.B.E., M.B., D.P.H.
W. M. Frazer, O.B.E., M.D., M.Sc., D.P.H.
E. H. R. Harries, M.D., F.R.C.P., D.P.H.
Professor A. Bradford Hill, D.Sc., Ph.D.
W. D. Hood, M.B., D.P.H.
J. R. Hutchinson, M.D., D.P.H.
Professor R. A. McCance, M.D., Ph.D., F.R.C.P.
Sir Alexander S. M. MacGregor, O.B.E., M.D., D.P.H., K.H.P.
R. H. Parry, M.D., F.R.C.P., D.P.H.

Professor R. M. F. Picken, M.B., D.P.H.
Professor J. C. Spence, M.C., M.D., F.R.C.P.
D. K. M. Chalmers, M.D., D.P.H. (*Secretary*).

## PROTEIN REQUIREMENTS

Professor H. P. Himsworth, M.D., F.R.C.P. (*Chairman*).
Professor A. C. Chibnall, Sc.D., F.R.S.
Professor S. J. Cowell, M.B., F.R.C.P.
R. Cruickshank, M.D., F.R.C.P.
C. R. Harington, Ph.D., F.R.S.
Professor R. A. McCance, M.D., Ph.D., F.R.C.P.
A. Neuberger, M.D., Ph.D.
Professor R. A. Peters, M.C., M.D., F.R.S.
Professor B. S. Platt, C.M.G., M.Sc., M.B., Ph.D.
Professor F. G. Young, D.Sc., Ph.D.
D. P. Cuthbertson, D.Sc., M.D. (*Secretary*).

## ROYAL NAVAL PERSONNEL RESEARCH COMMITTEE

Sir Edward Mellanby, K.C.B., M.D., Sc.D., F.R.C.P., F.R.S. (*Chairman*).
Captain J. R. S. Brown, R.N. (*October* 1943 *to October* 1944).
J. Buckingham.
Captain G. O. C. Davies, R.N. (*until March* 1943 *and also from February* 1945).
Surgeon Vice-Admiral Sir Sheldon Dudley, K.C.B., O.B.E., M.D., F.R.C.P., F.R.S., K.H.P.
Surgeon Captain R. A. Graff, M.R.C.S., L.R.C.P., R.N. (*from April* 1945).
Surgeon Commander E. James, M.D., M.R.C.P.E., R.N. (*from April* 1945).
Captain F. W. H. Jeans, R.N. (*March* 1943 *to December* 1944).
Captain R. Oliver-Bellasis, C.V.O., R.N. (*until March* 1943).
Captain H. K. P. Oram, R.N. (*from March* 1943).
Professor B. S. Platt, C.M.G., M.Sc., M.B., Ph.D.
Commander M. G. Rimington, D.S.O., R.N. (*from October* 1944).
A. Rodger, M.A. (*from April* 1945).
P. E. Vernon, Ph.D. (*until April* 1945).
G. L. Brown, C.B.E., M.Sc., M.B., F.R.S. (*Secretary*).
Surgeon Lieut. Commander F. P. Ellis, O.B.E., M.B., R.N. (*Naval Medical Secretary from January* 1944).

*Additional Members of Sub-Committees*

*Clothing*—

O. S. N. Richards (*Director of Victualling*), (*Chairman*).
T. Bedford, D.Sc., Ph.D.
R. B. Bourdillon, C.B.E., M.C., A.F.C., D.M.
F. Brookhouse.
J. C. D. Hutchinson, M.A.
O. M. Lidwell, D.Phil.
Commander H. C. Martell, R.N.
J. S. Weiner, M.Sc.
Lieut. Commander M. O. Pelton, R.N.V.R. (*Secretary*).

*Gunnery*—(*Secretary:* G. L. Brown, C.B.E., M.Sc., M.B., F.R.S.).
Commander (E) J. E. Goldby, R.N. (*Chairman*).
Lieut. Commander P. R. Bird, R.N. (*until October* 1944).
Lieut. Commander Sir Thomas Butler, Bt., R.N. (*October* 1944 *to February* 1945).
R. W. Cheshire.
Commander (E) A. B. Chibnall, R.N. (*January* 1944 *to August* 1944).
Professor W. E. le Gros Clark, D.Sc., F.R.C.S., F.R.S.
Lieut. Commander P. J. S. Hardinge, M.B.E., R.N. (*from February* 1945).
Lieut. Commander P. J. Hill-Norton, R.N. (*August* 1943 *to January* 1945).

E. O. Lemon.
Commander (E) J. E. H. Machen, R.N. (*from August* 1944).
Commander C. M. Parry, R.N. (*until August* 1943).
Commander M. J. Ross, D.S.C., R.N. (*from August* 1944).
Commander R. I. A. Sarell, D.S.O., R.N. (*from January* 1945).
A. J. Sims, R.C.N.C.
Lieut. Commander C. E. J. Streatfeild, R.N. (*from February* 1945).
Commander R. E. Washbourn, D.S.O., R.N. (*from November* 1944).
A. G. M. Weddell, M.D., D.Sc.

*Habitability*—(*Secretary:* Surgeon Lieut. Commander F. P. Ellis, O.B.E., M.B., R.N.).
Surgeon Captain M. Critchley, M.D., F.R.C.P., R.N.V.R. (*Chairman*).
T. Bedford, D.Sc., Ph.D.
M.G. Bennett.
R. C. Frederick.
Ezer Griffiths, D.Sc., F.R.S.
G. A. Knight.
B. McArdle, M.D., M.R.C.P.
N. H. Mackworth, M.B., Ch.B.
Commander R. I. A. Sarell, D.S.O., R.N.
A. J. Sims, R.C.N.C.
F. E. Smith (*from July* 1945).
Surgeon Commander G. H. G. Southwell-Sander, M.B., B.Ch., R.N.

*Underwater Physiology*—(*Chairman and Secretary:* G. L. Brown, C.B.E., M.Sc., M.B., F.R.S.)
Surgeon Lieut. Commander W. M. Davidson, M.B., B.Ch., R.N. (*from October* 1944).
Surgeon Lieut. Commander K. W. Donald, D.S.C., M.D., M.R.C.P., R.N.
Professor J. B. S. Haldane, M.A., F.R.S.
J. McAulay, D.Sc.
B. H. C. Matthews, C.B.E., Sc.D., F.R.S.
Surgeon Commander C. L. G. Pratt, O.B.E., M.D., M.Sc., R.N.V.R.
Commander W. O. Shelford, R.N.

*Visual Problems*—(*Secretary:* G. L. Brown, C.B.E., M.Sc., M.B., F.R.S.).
Surgeon Commander D. M. Beaton, O.B.E., R.N. (*Chairman*).
R. W. Cheshire.
Lieut. Commander M. O. Pelton, R.N.V.R.
E. E. Pochin, M.D., F.R.C.P.
Lieut. Commander T. E. F. Pooley, R.N.
Surgeon Lieut. Commander P. G. Rowsell, M.B., B.S., R.N.
W. S. Stiles, D.Sc., Ph.D., F.I.E.S.
P. E. Vernon, Ph.D.
W. D. Wright, Ph.D.

## SICKNESS RECORDING IN INDUSTRY

A. J. Amor, M.D., M.Sc. (*Chairman*).
R. B. Buzzard, B.M., B.Ch.
E. G. Chambers, M.A.
Mrs. Margaret Dobbie-Bateman, M.B., Ch.B.
Miss Vivien Glasspool.
M. W. Goldblatt, M.D., Ph.D.
S. A. Henry, M.D., F.R.C.P., D.P.H.
Professor A. Bradford Hill, D.Sc., Ph.D.
T. E. Howell, M.B., B.S.
Miss May Smith, D.Sc.
Miss Kathleen Turner, B.Sc.
S. Wyatt, D.Sc.
R. S. F. Schilling, M.B., B.S. (*Secretary*).

## STERILISATION OF SYRINGES

Professor G. S. Wilson, M.D., F.R.C.P., D.P.H., K.H.P. (*Chairman*).
V. D. Allison, M.D., D.P.H.
Professor H. Berry, B.Sc., F.R.I.C., Ph.C.
Professor A. D. Gardner, D.M., F.R.C.S.
Professor L. P. Garrod, M.D., F.R.C.P.
J. E. McCartney, D.Sc., M.D.
Professor J. McIntosh, M.D., LL.D.
A. A. Miles, F.R.C.P.
H. J. Parish, M.D., F.R.C.P.E.
E. T. C. Spooner, M.D. (*Secretary*).

## THERAPEUTIC REQUIREMENTS

Professor L. J. Witts, M.D., F.R.C.P. (*Chairman*)
Professor J. H. Burn, M.D., F.R.S.
Professor A. J. Clark, M.C., M.D., F.R.C.P., F.R.S.
C. E. Corfield, B.Sc., F.I.C., Ph.C.
H. Davis, B.Sc., Ph.D.
Professor J. A. Gunn, M.D., D.Sc., F.R.C.P.
P. Hamill, M.D., D.Sc., F.R.C.P.
R. D. Hutchinson, M.P.S.
J. M. Johnston, M.D., F.R.C.S.E.
W. P. Kennedy, B.Sc., Ph.D., L.R.C.P. & S.E.
A. Mortimer, O.B.E.
A. W. Thompson, M.B.E.
Professor G. H. Wooldridge, F.R.C.V.S.
C. H. Hampshire, M.B., B.Sc., Ph.C., F.R.I.C. (*Secretary*)

## TRAUMATIC SHOCK

Professor G. E. Gask, C.M.G., D.S.O., F.R.C.S. (*Chairman until February* 1940).
A. N. Drury, C.B.E., M.D., F.R.S. (*Chairman from February* 1940 *until March* 1943).
Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P. (*Chairman from March* 1943).
G. L. Brown, M.Sc., M.B., F.R.S.
Professor G. R. Cameron, D.Sc., M.B., F.R.C.P., F.R.S.
Sir Henry H. Dale, O.M., G.B.E., M.D., F.R.C.P., F.R.S.
Professor Sir Howard Florey, M.B., Ph.D., F.R.S.
Sir Claude Frankau, C.B.E., D.S.O., M.S., F.R.C.S.
Professor J. H. Gaddum, Sc.D., M.R.C.S., F.R.S.
R. T. Grant, O.B.E., M.D., M.R.C.P., F.R.S.
Professor H. N. Green, M.Sc., M.D. (*from February* 1944).
F. W. Holdsworth, M.Ch., F.R.C.S.
Surgeon Commander W. A. Hopkins, O.B.E., M.D., M.R.C.P.I., R.N. (*until January* 1945).
Surgeon Commander N. M. McArthur, M.D., R.N. (*from January* 1944).
Air Commodore R. R. Macintosh, D.M., F.R.C.S.E., D.A., R.A.F.V.R.
Professor J. McMichael, M.D., F.R.C.P.E.
Professor G. W. Pickering, M.B., F.R.C.P.
V. H. Riddell, M.D., F.R.C.S.
Professor J. A. Ryle, M.D., F.R.C.P. (*until April* 1943).
Brigadier Sir Lionel Whitby, C.V.O., M.C., M.D., F.R.C.P., R.A.M.C.
Professor W. C. Wilson, M.B., F.R.C.S.E.
Professor Sir Francis Fraser, M.D., F.R.C.P. (*Joint Secretary until September* 1943).
Professor B. A. McSwiney, Sc.D., M.B., F.R.S. (*Joint Secretary until September* 1943).
D. P. Cuthbertson, D.Sc., M.D. (*Secretary from September* 1943).

*Additional Members of Sub-Committees*

*Anaesthetics—*

J. Blomfield, O.B.E., M.D. (*Chairman*).
Brigadier A. S. Daly, F.R.C.S., D.A., *late* R.A.M.C.
C. Langton Hewer, M.B., D.A.
I. W. Magill, C.V.O., M.B., D.A.
M. D. Nosworthy, M.D., D.A.
G. S. W. Organe, M.D., D.A. (*Secretary*).

*Analytical Methods—*

C. R. Harington, Ph.D., F.R.S.
Professor H. Hartridge, M.D., D.Sc., F.R.S.
Professor E. J. King, Ph.D.
Miss J. M. Vaughan, O.B.E., F.R.C.P.
F. C. MacIntosh, Ph.D.
E. B. Reeve, B.M., M.R.C.P.
R. G. Macfarlane, M.D.

## TUBERCULOSIS IN WAR-TIME

The Viscount Dawson of Penn, P.C., G.C.V.O., K.C.B., M.D., F.R.C.P. (*Chairman*).
T. Stenner Evans, M.B., D.P.H.
Professor M. Greenwood, D.Sc., F.R.C.P., F.R.S.
F. R. G. Heaf, M.D., M.R.C.P.
G. G. Kayne, M.D., M.R.C.P., D.P.H.
Colonel Sir Alexander Russell, C.B.E., M.D., D.P.H., I.M.S. (*ret.*).
Miss May Smith, D.Sc.
Norman F. Smith, D.M.
Wing-Commander R. R. Trail, M.C., M.D., F.R.C.P., R.A.F.V.R.
Professor G. S. Wilson, M.D., F.R.C.P., D.P.H., K.H.P.
P. D'Arcy Hart, M.D., F.R.C.P. (*Secretary*).

*Additional Members of Sub-Committee*

*Mass Radiography*—(*Secretary:* P. D'Arcy Hart, M.D., F.R.C.P.).
S. Cochrane Shanks, M.D., F.R.C.P. F.F.R. (*Chairman*).
Miss K. C. Clark, M.B.E., F.S.R.
W. H. Coldwell, M.B., D.M.R.E., F.F.R.
Major P. Kerley, M.D., F.R.C.P., D.M.R.E., F.F.R., R.A.M.C.
Brigadier D. B. McGrigor, O.B.E., M.B., D.M.R.E., R.A.M.C.
Lieutenant G. B. Stanford, M.R.C.S., D.M.R.E., F.R.P.S., R.A.M.C.

## TYPHUS

Major General L. T. Poole, C.B., D.S.O., M.C., M.B., K.H.P., *late* R.A.M.C. (*Chairman*).
C. H. Andrewes, M.D., F.R.C.P., F.R.S.
Professor S. P. Bedson, M.D., M.Sc., F.R.C.P., F.R.S.
Lieut. Colonel H. J. Bensted, O.B.E., M.C., M.R.C.S., R.A.M.C.
Major General Sir Alexander Biggam, K.B.E., C.B., M.D., F.R.C.P., *late* R.A.M.C.
Professor P. A. Buxton, C.M.G., M.R.C.S., F.R.S.
Surgeon Commander D. Duncan, O.B.E., M.D., D.P.H., R.N.
Professor M. van den Ende, M.B., Ph.D.
A. Felix, D.Sc., F.R.S.
R. Lewthwaite, D.M., M.R.C.P.
M. D. Mackenzie, M.D., D.P.H.
Major K. Mellanby, Ph.D., R.A.M.C.
Major General D. T. Richardson, C.B., M.C., M.B., K.H.S., *late* R.A.M.C.
Air Marshal Sir Harold Whittingham, K.C.B., K.B.E., F.R.C.P., K.H.P., R.A.F.
F. Fulton, D.M. (*Secretary*).

## WAR WOUNDS

Sir Cuthbert Wallace, Bart., K.C.M.G., C.B., F.R.C.S. (*Chairman until his death in June*, 1944).
Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P. (*Chairman from June* 1944).
E. A. Carmichael, C.B.E., M.B., F.R.C.P.
L. Colebrook, M.B., F.R.C.O.G., F.R.S.
Brigadier F. A. E. Crew, M.D., D.Sc., F.R.S., R.A.M.C. (*from June* 1942).
A. N. Drury, C.B.E., M.D., F.R.C.P., F.R.S.
A. Tudor Edwards, M.D., F.R.C.S.
Sir Thomas Fairbank, D.S.O., O.B.E., M.S., F.R.C.S. (*from March* 1942).
Brigadier D. Fettes, O.B.E., M.B., F.R.C.S., *late* R.A.M.C. (*from February* 1945).
Professor Sir Howard Florey, M.B., Ph.D., F.R.S.
Sir Claude Frankau, C.B.E., D.S.O., M.S., F.R.C.S.
Professor Sir Francis Fraser, M.D., F.R.C.P.
Professor G. E. Gask, C.M.G., D.S.O., F.R.C.S.
G. R. Gridlestone, D.M., F.R.C.S. (*from January* 1942).
Surgeon Rear-Admiral Sir Gordon Gordon-Taylor, K.B.E., C.B., M.S., F.R.C.S.
Major-General Sir Charles Gordon-Watson, K.B.E., C.M.G., F.R.C.S., R.A.M.C.
Air Vice-Marshal G. L. Keynes, M.D., F.R.C.S., R.A.F.V.R.
Professor J. R. Learmonth, C.B.E., Ch.M., F.R.C.S.E.
Sir John C. G. Ledingham, C.M.G., D.Sc., F.R.C.P., F.R.S.
Professor J. McIntosh, M.D., LL.D.
Major General D. C. Monro, C.B., C.B.E., M.B., F.R.C.S.E., *late* R.A.M.C. (*from November* 1942 *to November* 1944).
Major General Sir Max Page, K.B.E., C.B., D.S.O., M.S., F.R.C.S., R.A.M.C.
G. Perkins, M.C., M.Ch., F.R.C.S. (*from January* 1942).
Major General H. Marrian Perry, C.B., O.B.E., F.R.C.P., *late* R.A.M.C. (*until September* 1942).
Professor R. S. Pilcher, M.S., M.R.C.P., F.R.C.S.
Major General L. T. Poole, D.S.O., M.C., K.H.P., *late* R.A.M.C. (*from September* 1942).
Professor J. Paterson Ross, M.S., F.R.C.S.
Professor J. A. Ryle, M.D., F.R.C.P. (*until April* 1943).
P. Jenner Verrall, M.B., F.R.C.S. (*until January* 1942).
Surgeon Rear Admiral Sir Cecil Wakeley, K.B.E., C.B., D.Sc., F.R.C.S. (*from January* 1942).
Sir Reginald Watson-Jones, M.Ch., F.R.C.S.
Colonel J. M. Weddell, C.B.E., F.R.C.S., *late* R.A.M.C. (*until November* 1942).
Professor W. W. C. Topley, M.D., F.R.C.P., F.R.S. (*Joint Secretary until July* 1941).
F. H. K. Green, M.D., F.R.C.P. (*Joint Secretary until July* 1941; *Secretary from July* 1941).

### *Additional Members of Sub-Committees*

*Anaerobic Wound Infections* ("*Anaerobes Sub-Committee*")—(*Chairman:* Major General L. T. Poole, D.S.O., M.C., K.H.P., *late* R.A.M.C.).
Professor R. V. Christie, D.Sc., M.D., F.R.C.P. (*from April* 1944).
Sir Percival Hartley, C.B.E., M.C., D.Sc., F.R.S.
W. E. van Heyningen, Ph.D.
Professor A. A. Miles F.R.C.P.
Miss Muriel Robertson, D.Sc., F.R.S.
B. W. Williams, M.B., F.R.C.S.
Miss Marjorie G. Macfarlane, D.Sc., Ph.D. (*Secretary*).

*Burns*—(*Chairman:* Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P.; *Secretary:* F. H. K. Green, M.D., F.R.C.P.).
R. B. Bourdillon, C.B.E., M.C., A.F.C., D.M.
Professor G. R. Cameron, D.Sc., F.R.C.P., F.R.S.
W. E. Chiesman, M.D., F.R.C.P.
A. M. Clark, M.C., Ch.M., F.R.F.P.S.
D. P. Cuthbertson, M.D., D.Sc.
Surgeon Captain A. Fairley, O.B.E., M.B., R.N.
Sir Harold Gillies, C.B.E., F.R.C.S.
Sir Archibald McIndoe, C.B.E., M.Sc., M.S., F.R.C.S.
F. J. McQuillin, B.Sc., D.Phil.
Professor R. A. Peters, M.C., M.D., F.R.S.
L. T. D. Williams, B.Sc., A.R.C.S.
Professor W. C. Wilson, M.B., F.R.C.S.E.

*Chest Injuries*—(*Chairman:* A. Tudor Edwards, M.D., F.R.C.S.).
P. R. Allison, Ch.M., B.Sc., F.R.C.S.
Surgeon Captain W. D. W. Brooks, D.M., F.R.C.P., R.N.
Clifford Hoyle, M.D., F.R.C.P.
Geoffrey Marshall, O.B.E., M.D., F.R.C.P.
T. Holmes Sellors, D.M., M.Ch., F.R.C.S.
O. S. Tubbs, M.B., F.R.C.S.
N. R. Barrett, M.Ch., F.R.C.S. (*Secretary*).

*Crush Injuries* (*Jointly with Traumatic Shock Committee*)—(*Chairman:* Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P.).
R. T. Grant, O.B.E., M.D., M.R.C.P., F.R.S.
Professor J. McMichael, M.D., F.R.C.P.E. (*Secretary*).

*Pathological Specimens*—(*Chairman:* Surgeon Rear-Admiral Sir Gordon Gordon-Taylor, K.B.E., C.B., M.S., F.R.C.S.; *Secretary:* F. H. K. Green, M.D., F.R.C.P.).
Professor W. G. Barnard, F.R.C.P.
Professor G. R. Cameron, D.Sc., F.R.C.P., F.R.S.
Professor G. Hadfield, M.D., F.R.C.P.
L. W. Proger, M.R.C.S., L.R.C.P.
Professor M. J. Stewart, M.B., F.R.C.P.
Miss Joan M. Ross, M.D.

*Vascular Injuries*—(*Chairman:* Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P.; *Secretary:* F. H. K. Green, M.D., F.R.C.P.).
Sir Thomas Lewis, C.B.E., M.D., F.R.C.P., F.R.S. (*Chairman until his death in March* 1945).
Air Commodore Sir Stanford Cade, K.B.E., C.B., F.R.C.S., R.A.F.V.R.
Sol M. Cohen, F.R.C.S.
Professor J. H. Gaddum, Sc.D., M.R.C.S., F.R.S.
Major D. L. Griffiths, M.B.E., M.B., F.R.C.S.
B. C. Maybury, M.B., F.R.C.S.
Professor Dorothy S. Russell, M.D., Sc.D., M.R.C.P.
E. D. Telford, M.Sc., F.R.C.S.

# APPENDIX II

# THE FLYING PERSONNEL RESEARCH COMMITTEE OF THE AIR MINISTRY

(Appointed January 1939)

## WAR-TIME MEMBERS OF MAIN COMMITTEE

Sir Edward Mellanby, K.C.B., M.D., Sc.D., F.R.C.P., F.R.S. (*Chairman*).
Professor F. C. Bartlett, C.B.E., M.A., F.R.S.
E. A. Carmichael, C.B.E., M.B., F.R.C.P.
C. S. Hallpike, M.B., F.R.C.S., F.R.C.P.
Professor A. Bradford Hill, D.Sc., Ph.D. (*from* 1942).
B. H. C. Matthews, C.B.E., Sc.D., F.R.S.
Sir John H. Parsons, C.B.E., D.Sc., M.B., F.R.C.S., F.R.S. (*retired* 1945).
Air Vice Marshal Sir Charles Symonds, K.B.E., C.B., M.D., F.R.C.P., R.A.F.V.R. (*from* 1943).
Professor L. J. Witts, M.D., F.R.C.P. (*ret.* 1942).
*Ex-officio members:—*
Air Marshal Sir Victor Richardson, K.B.E., C.B., M.B., K.H.S., R.A.F. (1939–41).
Air Marshal Sir Harold Whittingham, K.C.B., K.B.E., M.B., F.R.C.P., K.H.P., R.A.F. (*from* 1941).
Air Commodore H. E. Whittingham, C.B.E., M.B., F.R.C.P., R.A.F. (*Chief Executive Officer*) (*from* 1939–41).
Air Commodore T. McClurkin, M.B., B.Ch., R.A.F. (*Chief Executive Officer*) (*from* 1941).
Miss Isobel M. Marshall (*Secretary*).

## VISION COMMITTEE

(*February* 1941)

B. H. C. Matthews, C.B.E., Sc.D., F.R.S. (*Chairman*).
R. W. Cheshire, B.A.
K. J. W. Craik, Ph.D.
R. W. Ditchburn, B.Sc., Ph.D.
Brigadier Sir Stewart Duke-Elder, K.C.V.O., M.D., Ph.D., F.R.C.S.
Surgeon Commander C. F. Goodeve, F.R.S., R.N.V.R.
Squadron Leader E. A. G. Goldie, A.F.C., M.B., B.Ch., R.A.F.V.R.
M. Livesey.
Air Commodore P. C. Livingston, C.B., C.B.E., A.F.C., F.R.C.S.
Sir John H. Parsons, C.B.E., D.Sc., M.B., F.R.C.S., F.R.S.
E. E. Pochin, M.D., F.R.C.P.
T. Smith, M.A., F.R.S.
W. S. Stiles, D.Sc., Ph.D., F.I.E.S.
F. A. Vick, M.Sc., Ph.D., F.Inst.P.

## DAZZLE SUB-COMMITTEE

(*November* 1941)

W. S. Stiles, D.Sc., Ph.D., F.I.E.S. (*Chairman*).
K. J. W. Craik, Ph.D.
R. W. Ditchburn, B.Sc., Ph.D.
Captain S. G. Ferguson, R.A.
Squadron Leader E. A. G. Goldie, A.F.C., M.B., B.Ch., R.A.F.V.R.
Colonel G. H. Hinds, O.B.E.

Captain H. F. Howse, R.N.
J. W. Linnett, M.A., D.Phil.
Air Commodore P. C. Livingston, C.B., C.B.E., A.F.C., F.R.C.S.
Lieutenant H. A. C. McKay, R.N.V.R.
E. E. Pochin, M.D., F.R.C.P.
J. S. Preston, M.I.E.E., F.Inst.P.
R. F. Y. Randall, B.Sc.

## GOGGLES AND SPECTACLES SUB-COMMITTEE

(*February* 1944)

W. S. Stiles, D.Sc., Ph.D., F.I.E.S. (*Chairman*).
Major F. H. Coates.
Brigadier Sir Stewart Duke-Elder, K.C.V.O., M.D., Ph.D., F.R.C.S., R.A.M.C.
H. W. Hole.
Air Commodore P. C. Livingston, C.B., C.B.E., A.F.C., F.R.C.S.
M. Livesey.
F. A. Vick, M.Sc., Ph.D., F.Inst.P.
Squadron Leader E. A. G. Goldie, A.F.C., M.B., B.Ch., R.A.F.V.R.
J. Tunstead, M.A., Ph.D.
Sir Edward Penton, K.B.E.

## AIRSICKNESS COMMITTEE

(*November* 1940)

Professor L. J. Witts, M.D., F.R.C.P. (*Chairman*).
G. L. Brown, C.B.E., M.Sc., M.B., F.R.S.
E. A. Carmichael, C.B.E., M.B., F.R.C.P.
Surgeon Captain R. A. Graff, M.R.C.S., L.R.C.P., R.N.
C. S. Hallpike, M.B., F.R.C.S., F.R.C.P.
Air Commodore T. McClurkin, M.B., B.Ch., R.A.F.
Wing Commander R. H. Winfield, D.F.C., A.F.C., M.B., Ch.B., R.A.F.V.R.

## OTOLOGICAL SUB-COMMITTEE

(*February* 1943)

B. H. C. Matthews, C.B.E., Sc.D., F.R.S. (*Chairman*).
Air Commodore E. D. D. Dickson, C.B.E., M.B., F.R.C.S.E., D.L.O., K.H.S., R.A.F.
Surgeon Lieutenant Commander Gay French, R.N.
Squadron Leader D. B. Fry, Ph.D., R.A.F.V.R.
Squadron Leader J. E. G. McGibbon, O.B.E., M.B., B.S., D.L.O., R.A.F.V.R.
Flight Lieutenant G. E. Swindell, M.Sc., A.Inst.P., R.A.F.V.R.
E. J. Barnes.
A. W. G. Ewing, M.A., Ph.D.
C. S. Hallpike, M.B., F.R.C.S., F.R.C.P.
Wing Commander J. F. Simpson, F.R.C.S., R.A.F.V.R.
W. Makinson, M.Sc., A.M.I.E.E.
Brigadier M. L. Formby, M.B., F.R.C.S., R.A.M.C., (T.A.).
Surgeon Lieut. Commander S. C. Suggit, M.B., B.S., F.R.C.S., R.N.V.R. (*from* 1942).

## SUB-COMMITTEE ON ASSESSMENT OF TEMPERAMENT IN CONNEXION WITH AIRCREW SELECTION

(*May* 1943)

Professor F. C. Bartlett, C.B.E., M.A., F.R.S. (*Chairman*).
Professor E. A. Bott, O.B.E.
Air Commodore D. V. Carnegie, A.F.C., R.A.F.
Professor A. Bradford Hill, D.Sc., Ph.D.

Air Vice Marshal E. S. Goodwin, C.B.E., A.F.C.
Air Commodore R. D. Gillespie, M.D., F.R.C.P., R.A.F.V.R.
Air Vice Marshal Sir Charles Symonds, K.B.E., C.B., M.D., F.R.C.P., R.A.F.V.R.
Professor C. Roger Myers, M.A., Ph.D.
Group Captain G. R. Oliver, R.A.F.
Surgeon Lieut. Commander J. D. Simpson, M.D., R.N.V.R.
Air Marshal Sir Harold Whittingham, K.C.B., K.B.E., F.R.C.P., K.H.P., R.A.F.

## TECHNICAL ADVISORY SUB-GROUP OF THE SUB-COMMITTEE ON ASSESSMENT OF TEMPERAMENT IN CONNEXION WITH AIRCREW SELECTION

(*May* 1943)

Air Vice Marshal Sir Charles Symonds, K.B.E., C.B., M.D., F.R.C.P., R.A.F.V.R. (*Chairman*).
Professor F. C. Bartlett, C.B.E., M.A., F.R.S.
Air Commodore R. D. Gillespie, M.D., F.R.C.P.
Professor A. Bradford Hill, D.Sc., Ph.D.
Professor C. Roger Myers, M.A., Ph.D.

## FLYING PERSONNEL MEDICAL OFFICERS' MEETINGS

(*June* 1942)

Air Marshal Sir Harold Whittingham, K.C.B., K.B.E., M.B., F.R.C.P., K.H.P., R.A.F. (*Chairman*).
Wing Commander C. C. Barker, A.F.C., M.B., Ch.B., R.A.F.
Squadron Leader A. J. Barwood, M.R.C.S., L.R.C.P., R.A.F.
Flight Lieut. D. E. Breed, R.A.F.V.R.
Wing Commander E. B. Bright, A.F.C., M.B., Ch.B., R.A.F.
Wing Commander J. R. Cellars, A.F.C., M.B., Ch.B., R.A.F.
Wing Commander S. Davidson, A.F.C., F.R.C.S., R.A.F.V.R.
Wing Commander W. R. Franks, R.C.A.F.
Squadron Leader A. M. Fraser, R.C.A.F.
Wing Commander G. Gilchrist, M.B., B.S.
Squadron Leader J. C. Gilson, O.B.E., M.B., B.Chir., M.R.C.P., R.A.F.V.R.
Squadron Leader E. A. G. Goldie, A.F.C., M.A., M.B., B.Ch., R.A.F.V.R.
Squadron Leader W. Harvey, M.R.C.S., L.R.C.P., F.D.S., R.C.S., R.A.F.V.R.
Wing Commander J. P. Huins, O.B.E., A.F.C., B.Ch., M.R.C.S., L.R.C.P., R.A.F.
Wing Commander P. A. Lee, M.B., Ch.B., R.A.F.
Surgeon Lieut. Commander A. G. Macdonald, R.N.V.R.
Wing Commander T. C. Macdonald, A.F.C., M.D., D.P.H., R.A.F.
Air Commodore T. McClurkin, M.B., B.Ch., D.P.H., R.A.F.
B. H. C. Matthews, C.B.E., Sc.D., F.R.S.
Wing Commander R. Maycock, A.F.C., M.R.C.S., L.R.C.P., R.A.F.
G. M. Morant, D.Sc.
Wing Commander J. Park, M.B., Ch.B., R.A.F.
Squadron Leader E. A. Pask, O.B.E., M.B., Ch.B., D.A., R.A.F.V.R.
Wing Commander G. O. Williams, B.Sc., M.R.C.S., L.R.C.P., R.A.F.
Wing Commander O. S. M. Williams, M.R.C.S., L.R.C.P., D.A., R.A.F.
Wing Commander H. L. Roxburgh, O.B.E., Ph.D., B.Sc., M.B., Ch.B., R.A.F.
Wing Commander H. P. Ruffell Smith, A.F.C., M.B., B.Ch., R.A.F.
Wing Commander W. K. Stewart, A.F.C., B.Sc., M.B., Ch.B., R.A.F.
Wing Commander G. E. Watt, C.B.E., A.F.C., B.Eng., M.I.Mech.E., F.R.Ae.S., R.N.Z.A.F.
Squadron Leader B. J. O. Winfield, A.F.C., M.B., B.Ch., R.A.F.V.R.
Wing Commander R. H. Winfield, D.F.C., A.F.C., M.B., Ch.B., R.A.F.V.R.
Flying Officer J. D. B. Wilson, R.A.F.V.R.

*Allied Air Forces:*

Commandant Cohen, French Air Force.
Commandant Jacques Duguet, French Air Force.
Flight Lieut. K. Bazarnik, Polish Air Force.
Group Captain A. Fiumel, Polish Air Force.
Squadron Leader A. Luczak, Polish Air Force.
Commander A. J. Vorwald (MC) (USNR).
Colonel James J. Smith, U.S. Army Air Force.

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